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115610

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☐ N.A. Sequence
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STIC Search Report

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jan.delaval@uspto.gov

Search Notes

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FILE 'REGISTRY' ENTERED AT 07:06:59 ON 09 MAR 2004

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=> d ide can l27

L27 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2004 ACS on STN

RN 9002-04-4 REGISTRY

CN **Thrombin (8CI, 9CI)** (CA INDEX NAME)

OTHER NAMES:

CN Blood-coagulation factor II, activated

CN Blood-coagulation factor IIa

CN E.C. 3.4.21.5

CN E.C. 3.4.4.13

CN Factor IIa

CN Thrombase

CN Thrombin JMI

CN Thrombin-C

CN Thrombinar

CN Thrombofort

CN Thrombostat

CN Topical

CN Tropostasin

DR 8050-02-0, 8059-56-1, 9014-41-9, 105881-84-3, 53028-63-0

MF Unspecified

CI COM, MAN

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL

(*File contains numerically searchable property data)

Other Sources: EINECS**, TSCA**

(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

16660 REFERENCES IN FILE CA (1907 TO DATE)

857 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

16683 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:164226

REFERENCE 2: 140:161734

REFERENCE 3: 140:161624
 REFERENCE 4: 140:160166
 REFERENCE 5: 140:160143
 REFERENCE 6: 140:160116
 REFERENCE 7: 140:159934
 REFERENCE 8: 140:157747
 REFERENCE 9: 140:157441
 REFERENCE 10: 140:157149

=> d his

(FILE 'HOME' ENTERED AT 06:14:06 ON 09 MAR 2004)
 SET COST OFF

FILE 'HCAPLUS' ENTERED AT 06:14:23 ON 09 MAR 2004

L1 1 S US20020103107/PN
 E SOSLAU G/AU
 L2 42 S E3-E5
 E (GP OR GLYCOPROTEIN OR GLYCO PROTEIN) () (IB OR 1B OR (I OR 1) (
 L3 2133 S (GP OR GLYCOPROTEIN OR GLYCO PROTEIN) () (IB OR 1B OR (I OR 1) (
 E GLYCOPROTEIN/CT
 E E57+ALL
 L4 364 S E2
 L5 724 S GLYCOPROTEIN#/CW (L) (1B OR IB OR GP1B OR GPIB)
 E PAR/CT
 E E6+ALL
 L6 280 S E2
 L7 308 S E5
 L8 50 S E7
 L9 92 S E9
 L10 13417 S (PAR OR ((PROTEINASE OR PROTEASE) () ACTIVAT? () RECEPTOR) (5A) (1
 L11 13414 S (PAR OR ((PROTEINASE OR PROTEASE) () ACTIVAT? () RECEPTOR) () (1 OR
 L12 10684 S L10,L11 NOT RECEPTOR
 L13 2733 S L10,L11 NOT L12
 L14 4881 S L3-L9,L13
 E DRUG SCREENING/CT
 L15 22652 S E3-E5
 E E3+ALL
 L16 28787 S E2,E1+NT
 E E5+ALL
 L17 7824 S E3
 E E14+ALL
 L18 3025 S E1
 E E2+ALL
 E DRUG/CT
 E E10+ALL
 L19 15561 S E3
 E DRUG/CT
 L20 882 S E13
 L21 8110 S E230+NT OR E231
 L22 4500 S E262 OR E263
 E DRUG SCREENING+ALL/CT
 E E7+ALL
 L23 156 S E2

L24 78 S L14 AND L15-L23
L25 137 S L14 AND SCREEN?
L26 163 S L24,L25

FILE 'REGISTRY' ENTERED AT 06:26:53 ON 09 MAR 2004

L27 1 S THROMBIN/CN

FILE 'HCAPLUS' ENTERED AT 06:27:59 ON 09 MAR 2004

L28 16686 S L27
L29 31055 S THROMBIN
L30 118 S BLOOD() (COAGULAT? OR CLOT?) () FACTOR() (IIA OR II() ACTIVAT?)
L31 463 S THROMBASE OR THROMBINAR OR THROMBOFORT OR THROMBOSTAT OR TROP
L32 31683 S L28-L31
L33 48 S L26 AND L32
L34 33 S L26 AND PLATELET(L) AGGREGAT?
E CELL AGGREGATION/CT
L35 7 S E3,E4 AND L26
E E3+ALL
L36 15 S E1+NT AND L26
E PLATELET/CT
L37 30 S L26 AND E3-E27
E E28+ALL
L38 7 S L26 AND E3
E PLATELET/CT
E E33+ALL
L39 16 S L26 AND E6,E5
E E4+ALL
L40 27 S L26 AND E5,E4+NT
L41 40 S L26 AND (E12+NT OR E13+NT OR E14+NT)
L42 11 S L26 AND (E16+NT OR E17+NT)
L43 20 S L26 AND (ANTITHROMBO? OR ANTIPLATELET? OR ANTI() (THROMBO? OR
L44 92 S L33-L43
L45 1 S L2 AND L26
L46 1 S L2 AND L44
L47 1 S L1,L45,L46
L48 41 S L2 NOT L47
SEL DN AN 1 3 10 18
L49 4 S E1-E12 AND L48
L50 5 S L47,L49
L51 91 S L44 NOT L50
L52 32 S L41 AND (PY<=2000 OR PRY<=2000 OR AY<=2000)
SEL DN AN L52 4 7 19 26 28
L53 5 S E13-E27
L54 10 S L50,L53
L55 59 S L51 NOT L52-L54
SEL DN AN L55 7 14-18 23 27 29 30 32 33 35 40-43
L56 17 S E28-E70
L57 27 S L54,L56 AND L1-L26,L28-L56
L58 27 S L57 AND (PAR# OR PAR() (1 OR 2 OR 3 OR 4) OR PLATLET?(L) ACTIVA
L59 25 S L58 AND (INHIBIT? OR BLOCK? OR ANTAGON?)
L60 27 S L58,L59

FILE 'REGISTRY' ENTERED AT 07:06:59 ON 09 MAR 2004

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 07:07:09 ON 09 MAR 2004

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FILE LAST UPDATED: 8 Mar 2004 (20040308/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d 160 all tot

L60 ANSWER 1 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:736673 HCAPLUS
DN 140:14987
ED Entered STN: 19 Sep 2003
TI **Proteinase-activated receptors (PARs)**
), **platelets** and angiogenesis
AU Perini, Rafael; Wallace, John L.
CS Mucosal Inflammation Research Group, University of Calgary, Calgary, AB, Can.
SO Drug Development Research (2003), 59(4), 395-399
CODEN: DDREDK; ISSN: 0272-4391
PB Wiley-Liss, Inc.
DT Journal; General Review
LA English
CC 13-0 (Mammalian Biochemistry)
Section cross-reference(s): 1, 2
AB A review. With respect to the role of **proteinase-activated receptors (PARs)**, few cells have been as thoroughly studied as the **platelet**. **PARs** appear to act as the key **receptors** mediating the pro-**aggregatory** and pro-secretory effects of **thrombin**, but there is considerable variation from species to species in terms of which **PARs** are involved in these processes. In addition to contributing to hemostasis, **platelets** are increasingly being viewed as important contributors to healing and to tumor growth. This can be attributed to the many pro- and anti-angiogenic factors that are stored within **platelets** and are released as sites of injury and new vessel growth. There is emerging evidence for an important role for **PARs** in regulating the release of growth factors from **platelets**, raising the specter that **PARs** may be a rational target for new therapies that will modulate repair processes and tumor growth.
ST review **proteinase activated receptor**
platelet angiogenesis
IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**PAR (proteinase-activated**
receptors); **proteinase-activated**
receptors and **platelets** and angiogenesis)
IT Angiogenesis
Drug targets
Platelet (blood)
(**proteinase-activated receptors** and
platelets and angiogenesis)
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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L60 ANSWER 2 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:262709 HCAPLUS
DN 139:127224
ED Entered STN: 06 Apr 2003
TI **Protease-activated receptor-2**
antagonists and agonists
AU Scarborough, Robert M.
CS Cardiovascular Chemistry, Millennium Pharmaceuticals, Inc., S. San
Francisco, CA, 94080, USA
SO Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003),
1(1), 73-82
CODEN: CMCCDP; ISSN: 1568-0169
PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review. Interest in the development of specific **antagonists**
of the **protease-activated receptors** are
significant, however, achieving such goals remain extremely challenging.
Considerable efforts have been directed at developing specific
antagonists of the first elucidated member of this
receptor family, namely the **thrombin receptor**,
PAR-1. However, significantly less effort has been
directed at the second member of the family, **PAR-2** due
in **part** to lack of clarity concerning its **activating**
protease(s), and uncertainty concerning its **physiol.** and
pathophysiol. roles in disease pathways. This review will briefly
summarize what is known about the **activating protease**
(s), the potential (patho)physiol. roles for **PAR-2** and
structure-activity relationships that have been developed for **PAR**

-2 agonists and antagonists in relationship to agonists and antagonists developed for the other protease-activated receptors.

ST review protease activated receptor antagonist agonist drug target

IT Receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PAR-2 (proteinase-activated receptor 2); structure-activity relationships of protease-activated receptor-2 antagonists and agonists)

IT Drug targets

Human

Structure-activity relationship

(structure-activity relationships of protease-activated receptor-2 antagonists and agonists)

RE.CNT 93 THERE ARE 93 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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L60 ANSWER 3 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:262707 HCAPLUS

DN 139:127222

ED Entered STN: 06 Apr 2003

TI Non-peptidic small-molecule antagonists of the human
platelet thrombin receptor PAR-
1

AU Selnick, H. G.; Barrow, J. C.; Nantermet, P. G.; Connolly, T. M.

CS Department of Medicinal Chemistry, Merck Research Laboratories, West
Point, PA, 19486, USA

SO Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003),
1(1), 47-59

CODEN: CMCCDP; ISSN: 1568-0169

PB Bentham Science Publishers Ltd.

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review. The **thrombin receptor** on human**platelets** is the first member identified of a new family of G-protein coupled **receptors** referred to as **protease activated receptors (PARs)**. These**receptors** are **activated** by a unique mechanism involving proteolytic cleavage of a portion of the extracellular domain to generate a new N-terminus which then acts as a **tethered** or intramol.ligand (agonist) for the **receptor**. The hexapeptide SFLLRN-NH₂ comprising the new N-terminus is referred to as the **Thrombin****Receptor Activating Peptide**, or "TRAP" **Thrombin**is the most potent agonist for **platelet aggregation**and selective **blockade** of the intramol. **activation**step without effecting the proteolytic activity of **thrombin**should result in moderation of **platelet activation** and**aggregation** without interfering with the other coagulation cascadeeffects of **thrombin**. **Screening** of combinatoriallibraries identified a novel, non-peptide **PAR-1****thrombin receptor antagonist**. Examination of

structure-activity relationships revealed that portions of the mol. could

be replaced resulting in simpler mols. of lower mol. weight that were at the

same time more potent. Mols. in this series were effective

antagonists of TRAP-stimulated **platelet****activation**, but had limited activity when **thrombin** wasthe agonist. Addnl. directed **screening** and subsequent lead

refinement resulted in a second series of isoxazole based compds. Some of

the resultant mols. were potent **PAR-1****antagonists** that were effective against both TRAP- and**thrombin-stimulated receptor activation**.These compds. do not **inhibit** the proteolytic effects of**thrombin** but rather interfere with the intramol. binding of the**tethered** ligand (SFLLRN) to the transmembrane portion of the**thrombin receptor**. They represent promising leads forfuture explorations of **antithrombotic** activity of**thrombin receptor antagonists**.ST review nonpeptide mol **antagonist antiplatelet****thrombin receptor PAR1**IT **Receptors**

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(PAR-1 (protease-activated

receptor 1); non-peptidic small-mol.

antagonists of human **platelet thrombin**

receptor PAR-1)

IT **Anticoagulants**

Combinatorial library

Drug screening

Human

Platelet aggregation inhibitors

Structure-activity relationship

(non-peptidic small-mol. **antagonists** of human**platelet thrombin receptor PAR-**

1)

IT **9002-04-4, Thrombin**

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(non-peptidic small-mol. **antagonists** of human**platelet thrombin receptor PAR-**

1)

RE.CNT 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L60 ANSWER 4 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:262705 HCAPLUS

DN 139:127220

ED Entered STN: 06 Apr 2003

TI Discovery of potent peptide-mimetic antagonists for the human
thrombin receptor, protease-activated
receptor-1 (PAR-1)

AU Maryanoff, Bruce E.; Zhang, Han-Cheng; Andrade-Gordon, Patricia; Derian,
Claudia K.

CS Drug Discovery, Johnson and Johnson Pharmaceutical Research and
Development, Spring House, PA, 19477-0776, USA

SO Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003),
1(1), 13-36

CODEN: CMCCDP; ISSN: 1568-0169

PB Bentham Science Publishers Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 27, 28, 34
AB A review. **Protease-activated receptors (PARs)** represent a unique family of seven-transmembrane G-protein-coupled **receptors**, which are enzymically cleaved to expose a new extracellular N-terminus that acts as a **tethered activating** ligand. **PAR-1** is cleaved and **activated** by the serine **protease α -thrombin**, is expressed in various tissues (e.g., **platelets** and vascular cells), and is involved in cellular responses associated with hemostasis, proliferation, and tissue injury. By using a de novo design approach, we have discovered a series of potent heterocycle-based peptide-mimetic **antagonists** of **PAR-1**, exemplified by advanced leads RWJ-56110 and RWJ-58259. These compds. are potent, selective **PAR-1 antagonists**, devoid of **PAR-1** agonist and **thrombin inhibitory** activity: they bind to **PAR-1**, interfere with calcium mobilization and cellular functions associated with **PAR-1**, and do not affect **PAR-2**, **PAR-3**, or **PAR-4**. RWJ-56110 was determined to be a direct **inhibitor** of **PAR-1** **activation** and internalization, without affecting **PAR-1** N-terminal cleavage. At high concns. of **α -thrombin**, RWJ-56110 fully **blocked activation** responses in human vascular cells, but not in human **platelets**; whereas, at high concns. of TRAP-6, RWJ-56110 **blocked activation** responses in both cell types. This result is consistent with the presence of another **thrombin receptor** on human **platelets**, namely **PAR-4**. RWJ-56110 and RWJ-58259 clearly interrupt the binding of a **tethered** ligand to its **receptor**. RWJ-58259 demonstrated antirestenotic activity in a rat balloon angioplasty model and **antithrombotic** activity in a cynomolgus monkey arterial injury model. Such **PAR-1 antagonists** should not only serve as useful tools to delineate the physiol. and pathophysiol. roles of **PAR-1**, but also may have therapeutic potential for treating thrombosis and restenosis in humans.

ST review peptidomimetic **thrombin receptor antagonist** **protease PAR1** **antithrombotic** restenosis

IT **Receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**PAR-1 (proteinase-activated receptor 1)**); discovery of potent peptide-mimetic **antagonists** for human **thrombin receptor**, **protease-activated receptor-1 (PAR-1)**)

IT Artery
(angioplasty; discovery of potent peptide-mimetic **antagonists** for human **thrombin receptor**, **protease-activated receptor-1 (PAR-1)**)

IT Peptidomimetics
(**antagonists**; discovery of potent peptide-mimetic **antagonists** for human **thrombin receptor**, **protease-activated receptor-1 (PAR-1)**)

IT **Anticoagulants**
Drug design
Human

Thrombosis

(discovery of potent peptide-mimetic antagonists for human thrombin receptor, protease-activated receptor-1 (PAR-1))

IT Artery, disease

(restenosis; discovery of potent peptide-mimetic antagonists for human thrombin receptor, protease-activated receptor-1 (PAR-1))

IT 252889-88-6, RWJ-56110 315203-31-7, RWJ-58259

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(discovery of potent peptide-mimetic antagonists for human thrombin receptor, protease-activated receptor-1 (PAR-1))

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L60 ANSWER 5 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:262704 HCAPLUS

DN 139:127219

ED Entered STN: 06 Apr 2003

TI Peptide-derived **protease-activated receptor-1 (PAR-1) antagonists**

AU Seiler, Steven M.; Bernatowicz, Michael S.

CS Department of Vascular Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08534, USA

SO Current Medicinal Chemistry: Cardiovascular & Hematological Agents (2003), 1(1), 1-11

CODEN: CMCCDP; ISSN: 1568-0169

PB Bentham Science Publishers Ltd.

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

Section cross-reference(s): 34

AB A review. **Protease activated receptor-**

1 (PAR-1) is a G-coupled receptor

cleaved by **thrombin** and other **proteases** to expose a

new N-terminus, a "**tethered ligand**", that **activates**

the **receptor**. Independently of proteolytic cleavage, peptides

similar to the new N-terminus also **activate** the **receptor**

, and structure activity relationships for the **activating**

peptides have been extensively studied. Modification of

activating peptides led to rationally designed peptide

antagonists. The more potent peptide **antagonists** were

N-terminal and 3-position modifications of the agonist peptides. The resulting **PAR-1 antagonists** have proved useful in pharmacol. studies resolving the contribution of **PAR-1** signaling mechanisms relative to other **PARs** in **platelets**, vascular endothelial and other cell types. High affinity peptide agonists and **antagonists** have been radiolabeled and proven useful in binding assays. **Screening** of combinatorial libraries and compound collections using the radioligands have identified non-peptide **antagonists** of several different chemotypes. When the "**thrombin receptor**" (**PAR-1**) was first cloned and its mechanism of **activation** elucidated, there was great enthusiasm for the **receptor** as a drug target. The use of peptide agonists and **antagonists** has made possible much progress in our understanding of the role of this **receptor**.

ST review peptide **protease receptor PAR1**
antagonist structure activity thrombosis

IT **Receptors**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (PAR-1 (proteinase-activated
 receptor 1); structure-activity relationship of
 peptide-derived **protease-activated receptor**
 -1 (PAR-1) **antagonists**)

IT **Thrombosis**

(arterial; structure-activity relationship of peptide-derived
protease-activated receptor-1 (
 PAR-1) **antagonists**)

IT Artery, disease

(restenosis; structure-activity relationship of peptide-derived
protease-activated receptor-1 (
 PAR-1) **antagonists**)

IT Combinatorial library

Drug screening

Human

Peptide library

Signal transduction, biological

Structure-activity relationship

(structure-activity relationship of peptide-derived **protease-**
activated receptor-1 (PAR-
 1) **antagonists**)

IT 322765-75-3, BMS-200261

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
 (Biological study); USES (Uses)

(structure-activity relationship of peptide-derived **protease-**
activated receptor-1 (PAR-
 1) **antagonists**)

RE.CNT 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L60 ANSWER 6 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:184200 HCAPLUS

ED Entered STN: 11 Mar 2003

TI Discovery and optimization of potent orally active small molecular
thrombin receptor PAR-1
antagonists

AU Kawahara, Tetsuya; Suzuki, Syuichi; Kogushi, Motoji; Matsuoka, Toshiyuki;
Kobayashi, Hiroko; Kajiwaru, Akiharu; Hishinuma, Ieharu

CS Drug research laboratory, Eisai Co., Ltd, Tukuba, 300-2635, Japan

SO Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23-27, 2003 (2003), MEDI-234 Publisher: American Chemical Society, Washington, D. C.
CODEN: 69DSA4
DT Conference; Meeting Abstract
LA English
AB **Thrombin**, a trypsin-like serine **protease**, is centrally involved in hemostasis, and also promotes diverse cellular responses such as **platelet aggregation**, lymphocyte mitosis, monocyte chemotaxis, and vascular smooth muscle proliferation. These actions are mediated by proteolytically-activated **thrombin receptors (protease-activated receptors: PARs)**. A non-peptide small mol. **PAR-1 antagonist** (ER-97719-15) was obtained from high throughput **screening** using a **receptor binding** assay system. Through optimization of ER-97719-15, we found three types of compound with moderate **PAR-1 antagonistic** activity. In particular the indolin derivative ER-121958-06 **inhibited** human PRP **aggregation** by **thrombin** at 21nM. Furthermore ER-121958-06 (10 mg/kg p.o.) **inhibited** ex vivo **aggregation** induced by **thrombin** in the guinea pig. The SAR and biol. evaluation of this series of compds. are described.

L60 ANSWER 7 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:696020 HCAPLUS
DN 137:227727
ED Entered STN: 13 Sep 2002
TI Protein, gene and cDNA sequences of a novel guinea pig **proteinase-activated receptor 4 (PAR-4)** and its **activating peptide**
IN Darrow, Andrew; Derian, Claudia; Addo, Michael; Andrade-Gordon, Patricia
PA Ortho-McNeil Pharmaceutical, Inc., USA
SO PCT Int. Appl., 63 pp.
CODEN: PIXXD2

DT Patent
LA English
IC ICM C07K014-705
ICS C12N015-12; C07K016-28; G01N033-50; C12N005-10
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 6, 13

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|----------------|--|----------|-----------------|----------|
| PI | WO 2002070564 | A2 | 20020912 | WO 2002-US5946 | 20020226 |
| | WO 2002070564 | A3 | 20030227 | | |
| | W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| | RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| | EP 1363947 | A2 | 20031126 | EP 2002-713702 | 20020226 |
| | R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| PRAI | US 2001-798279 | A | 20010302 | | |
| | WO 2002-US5946 | W | 20020226 | | |

AB This invention provides protein, gene and cDNA sequences of a novel guinea pig **PAR-4** and its **activating peptide**. The guinea pig DNA and protein are useful for the development of models of human **platelet aggregation**. The invention further

relates to an animal model to assess the role of **PAR antagonists** in thrombosis.

ST gene cDNA sequence *Cavia* **proteinase activated receptor PAR4**

IT **Receptors**

RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)

(**PAR-4 (proteinase-activated receptor 4)**; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4 (PAR-4)** and its activating peptide)

IT **Platelet (blood)**

(**aggregation, PAR-4 inducing**; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4 (PAR-4)** and its activating peptide)

IT Gene, animal

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(encoding **PAR-4**; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4 (PAR-4)** and its activating peptide)

IT Genetic vectors

(for expressing **PAR-4**; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4 (PAR-4)** and its activating peptide)

IT Antibodies

RL: BSU (Biological study, unclassified); BIOL (Biological study) (monoclonal, to **PAR-4**; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4 (PAR-4)** and its activating peptide)

IT **Drug screening**

Guinea pig (*Cavia porcellus*)

Human

Molecular cloning

Protein sequences

cDNA sequences

(protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4 (PAR-4)** and its activating peptide)

IT Antibodies

RL: BSU (Biological study, unclassified); BIOL (Biological study) (to **PAR-4**; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4 (PAR-4)** and its activating peptide)

IT 459226-13-2P

RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)

(amino acid sequence; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4 (PAR-4)** and its activating peptide)

IT 459226-10-9

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(amino acid sequence; protein, gene and cDNA sequences of novel guinea pig **proteinase-activated receptor 4 (PAR-4)** and its activating

peptide)

IT 58-64-0, ADP, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (degranulation; protein, gene and cDNA sequences of novel guinea pig
proteinase-activated receptor 4 (
PAR-4) and its **activating peptide)**

IT 7440-70-2, Calcium, biological studies
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (mobilization; protein, gene and cDNA sequences of novel guinea pig
proteinase-activated receptor 4 (
PAR-4) and its **activating peptide)**

IT 459226-11-0P 459226-12-1P
 RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified);
 PRP (Properties); BIOL (Biological study); PREP (Preparation)
 (nucleotide sequence; protein, gene and cDNA sequences of novel guinea
 pig **proteinase-activated receptor**
4 (PAR-4) and its **activating**
peptide)

IT 212277-69-5, GenBank AF080215 385282-18-8, GenBank AF055917
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
 (Biological study)
 (protein, gene and cDNA sequences of a novel guinea pig
proteinase-activated receptor 4 (
PAR-4) and its **activating peptide)**

IT 459232-25-8 459232-26-9
 RL: PRP (Properties)
 (unclaimed nucleotide sequence; protein, gene and cDNA sequences of a
 novel guinea pig **proteinase-activated**
receptor 4 (PAR-4) and its
activating peptide)

IT 459232-27-0 459232-28-1 459232-29-2
 RL: PRP (Properties)
 (unclaimed protein sequence; protein, gene and cDNA sequences of a
 novel guinea pig **proteinase-activated**
receptor 4 (PAR-4) and its
activating peptide)

IT 141136-83-6 213018-42-9 225779-44-2 459123-98-9 459123-99-0
 RL: PRP (Properties)
 (unclaimed sequence; protein, gene and cDNA sequences of a novel guinea
 pig **proteinase-activated receptor**
4 (PAR-4) and its **activating**
peptide)

L60 ANSWER 8 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 2002:675811 HCAPLUS
 DN 137:195614
 ED Entered STN: 08 Sep 2002
 TI Compositions and methods for preventing platelet
aggregation comprising histones
 IN Class, Reiner; **Soslau, Gerald**; Zeppezauer, Michael
 PA Philadelphia, Health and Education Corporation, USA; Symbiotec G.m.b.H.
 SO PCT Int. Appl., 13 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A61K009-70
 ICS A61K009-22; A61K031-00; A61K051-08; A61K009-50; A61F002-00;
 B01J013-08; C12N011-02
 CC 1-12 (Pharmacology)
 FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|----|---------------|------|----------|-----------------|----------|
| PI | WO 2002067907 | A1 | 20020906 | WO 2002-US5157 | 20020222 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1370248 A1 20031217 EP 2002-706353 20020222

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRAI US 2001-270759P P 20010222

WO 2002-US5157 W 20020222

AB Compns. and methods for preventing **platelet aggregation**
and treating cardiovascular disease via histone compds. are provided. An
assay for **platelet aggregation** using angonist and
antagonist is described.

ST **platelet aggregation inhibitor histone**

IT Histones

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(H1; compns. and methods for preventing **platelet
aggregation**)

IT Histones

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(H2A; compns. and methods for preventing **platelet
aggregation**)

IT Histones

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(H2B; compns. and methods for preventing **platelet
aggregation**)

IT Histones

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(H3; compns. and methods for preventing **platelet
aggregation**)

IT Histones

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(H4; compns. and methods for preventing **platelet
aggregation**)

IT **Platelet aggregation inhibitors**

(compns. and methods for preventing **platelet
aggregation**)

IT Histones

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)

(compns. and methods for preventing **platelet
aggregation**)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Hale; US 5607691 A 1997 HCAPLUS

(2) Ito; US 5126140 A 1992 HCAPLUS

(3) Yen; US 5616311 A 1997 HCAPLUS

L60 ANSWER 9 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:575738 HCAPLUS

DN 137:103859

ED Entered STN: 02 Aug 2002

TI Screening assay for anti-thrombotic/
anti-platelet activity

IN Soslau, Gerald

PA USA

SO U.S. Pat. Appl. Publ., 5 pp.

CODEN: USXXCO

DT Patent

LA English

IC ICM C12Q001-56

ICS A61K031-00

NCL 514001000

CC 1-1 (Pharmacology)

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|-----------------|------|----------|-----------------|--------------|
| PI | US 2002103107 | A1 | 20020801 | US 2001-29611 | 20011221 <-- |
| PRAI | US 2000-257067P | P | 20001221 | | |

AB A method for screening for anti-thrombotic/
anti-platelet agents is provided where the method is
based on inhibition of the GP Ib,
PAR-1 and/or PAR-4 pathways by the
potential antithrombotic/anti-platelet
agent.

ST screening assay thrombotic platelet activity

IT Glycoproteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GPIb; screening assay for anti-
thrombotic/anti-platelet activity)

IT Receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PAR-1 (proteinase-activated
receptor 1); screening assay for
anti-thrombotic/anti-platelet
activity)

IT Receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(PAR-4 (proteinase-activated
receptor 4); screening assay for
anti-thrombotic/anti-platelet
activity)

IT Platelet (blood)

(aggregation; screening assay for anti-
thrombotic/anti-platelet activity)

IT Biological transport

(efflux; screening assay for anti-
thrombotic/anti-platelet activity)

IT Cell aggregation

(platelet; screening assay for anti-
thrombotic/anti-platelet activity)

IT Anticoagulants

Drug screening

Platelet (blood)

Platelet aggregation inhibitors

(screening assay for anti-thrombotic/
anti-platelet activity)

IT 56-65-5, 5'-ATP, biological studies 7440-70-2, Calcium, biological
studies 9002-04-4, Thrombin

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(screening assay for anti-thrombotic/
anti-platelet activity)

L60 ANSWER 10 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:171599 HCAPLUS

DN 136:226788
 ED Entered STN: 08 Mar 2002
 TI Therapeutics and diagnostics based on a novel signal transduction system
 in **platelets**
 IN Ramakrishnan, Vanitha; Phillips, David
 PA Cor Therapeutics, Inc., USA
 SO PCT Int. Appl., 64 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM A01K067-027
 ICS G01N033-86; A61P007-00
 CC 1-8 (Pharmacology)
 Section cross-reference(s): 9, 15

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|--|--|--------------|-----------------|--------------|
| PI | WO 2002017711 | A2 | 20020307 | WO 2001-US26936 | 20010831 <-- |
| | WO 2002017711 | A3 | 20030227 | | |
| | WO 2002017711 | C2 | 20031030 | | |
| | W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | |
| | RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | |
| | AU 2001086900 | A5 | 20020313 | AU 2001-86900 | 20010831 <-- |
| PRAI | US 2000-229047P | P | 20000831 <-- | | |
| | US 2000-230566P | P | 20000831 <-- | | |
| | WO 2001-US26936 | W | 20010831 | | |
| AB | The present invention relates to therapeutics and diagnostics that take advantage of a novel signal transduction pathway in platelets . In addition, the present invention provides methods for identifying agents that modulate activities mediated by the novel transduction pathway including platelet activation and thrombosis. | | | | |
| ST | signal transduction blood platelet sequence glycoprotein | | | | |
| IT | GPV diagnostic antithrombotic | | | | |
| IT | CD antigens | | | | |
| | RL: BSU (Biological study, unclassified); BIOL (Biological study) (CD42a; antithromotics and diagnostics based on a novel signal transduction system in platelets) | | | | |
| IT | Cytometry | | | | |
| | (FACS (fluorescence- activated cell sorting); antithromotics and diagnostics based on a novel signal transduction system in platelets) | | | | |
| IT | Glycoproteins | | | | |
| | RL: BSU (Biological study, unclassified); BIOL (Biological study) (GP IX ; antithromotics and diagnostics based on a novel signal transduction system in platelets) | | | | |
| IT | Platelet (blood) | | | | |
| | (GP V-null; antithromotics and diagnostics based on a novel signal transduction system in platelets) | | | | |
| IT | Glycoproteins | | | | |
| | RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses) (GP Vfl ; antithromotics and diagnostics based on a novel signal transduction system in platelets) | | | | |
| IT | Glycoproteins | | | | |
| | RL: BSU (Biological study, unclassified); BIOL (Biological study) (GP1b ; antithromotics and diagnostics based on a novel signal | | | | |

- transduction system in **platelets**)
- IT **Glycoproteins**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(V; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT **Platelet (blood)**
(**activation**; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT **Diagnosis**
(agents; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT **Transgene**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(animal expressing; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT **Anticoagulants**
Blood analysis
 Blood coagulation
Diagnosis
Drug delivery systems
 Drug screening
Genetic vectors
Molecular cloning
Mouse
 Platelet aggregation inhibitors
Protein sequences
Rabbit
Signal transduction, biological
cDNA sequences
 (antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT **Thrombin receptors**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT **Antibodies**
RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT **Mutation**
(deletion, knockout; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT **Immunoassay**
(immunoblotting; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT **Animal**
(transgenic GP V knockout; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT 71142-71-7, Ppack
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(-inactivated **thrombin**; antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT 9002-04-4, **Thrombin**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT 9002-04-4D, **Thrombin**, analogs
RL: PAC (Pharmacological activity); BIOL (Biological study)
(antithromotics and diagnostics based on a novel signal transduction system in **platelets**)
- IT 402907-62-4

RL: PRP (Properties)

(unclaimed nucleotide sequence; therapeutics and diagnostics based on a novel signal transduction system in **platelets**)

IT 402907-63-5

RL: PRP (Properties)

(unclaimed protein sequence; therapeutics and diagnostics based on a novel signal transduction system in **platelets**)

IT 259085-34-2 259085-35-3 259085-36-4 259085-37-5 259085-38-6

402907-57-7 402907-58-8 402907-59-9 402907-60-2 402907-61-3

402907-64-6 402907-65-7

RL: PRP (Properties)

(unclaimed sequence; therapeutics and diagnostics based on a novel signal transduction system in **platelets**)

L60 ANSWER 11 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:746574 HCAPLUS

DN 136:112200

ED Entered STN: 12 Oct 2001

TI Discovery and initial structure-activity relationships of trisubstituted ureas as **thrombin receptor (PAR-1) antagonists**

AU Barrow, J. C.; Nantermet, P. G.; Selnick, H. G.; Glass, K. L.; Ngo, P. L.; Young, M. B.; Pellicore, J. M.; Breslin, M. J.; Hutchinson, J. H.; Freidinger, R. M.; Condra, C.; Karczewski, J.; Bednar, R. A.; Gaul, S. L.; Stern, A.; Gould, R.; Connolly, T. M.

CS Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA

SO Bioorganic & Medicinal Chemistry Letters (2001), 11(20), 2691-2696

CODEN: BMCLE8; ISSN: 0960-894X

PB Elsevier Science Ltd.

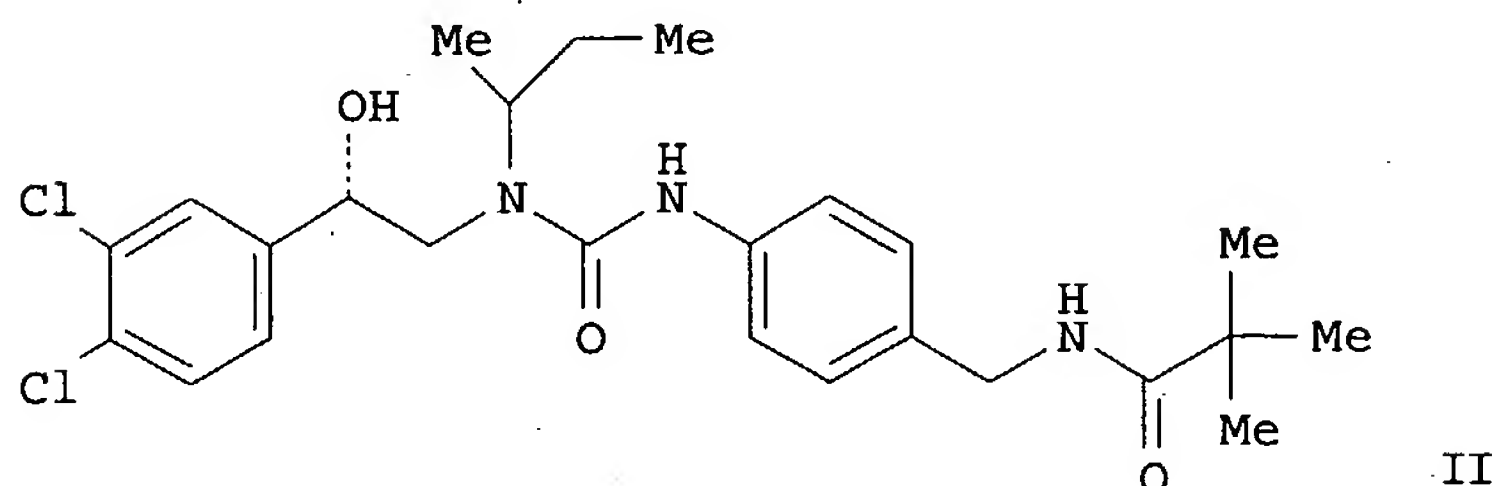
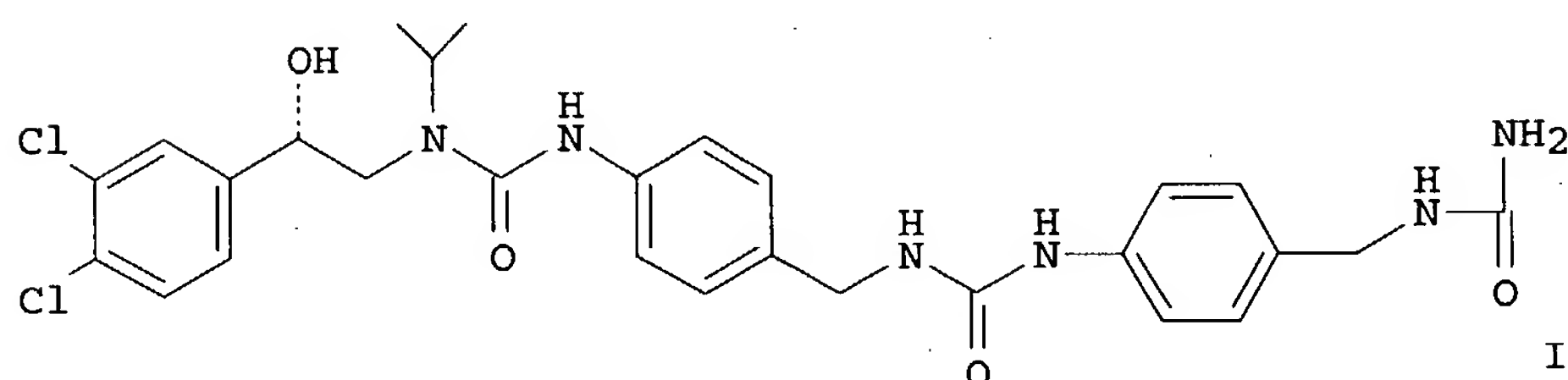
DT Journal

LA English

CC 1-3 (Pharmacology)

Section cross-reference(s): 25, 27, 28, 34

GI



- AB **Thrombin is the most potent agonist of platelet activation, and its effects are predominantly mediated by platelet thrombin receptors. Therefore, antagonists of the thrombin receptor have potential utility for the treatment of thrombotic disorders. Screening of combinatorial libraries revealed (I) to be a potent antagonist of the thrombin receptor. Modifications of this structure produced (II), which inhibits thrombin receptor stimulated secretion and aggregation of platelets.**
- ST **antiplatelet trisubstituted ureas PAR1 receptor antagonist structure; thrombin receptor antagonist structure trisubstituted ureas**
- IT **Receptors**
 RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (PAR-1 (proteinase-activated receptor 1), antagonists; discovery and structure-activity relationships of trisubstituted ureas as thrombin receptor (PAR-1) antagonists)
- IT **Structure-activity relationship (PAR-1 receptor-antagonizing; discovery and structure-activity relationships of trisubstituted ureas as thrombin receptor (PAR-1) antagonists)**
- IT **Thrombin receptors**
 RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (antagonists; discovery and structure-activity relationships of trisubstituted ureas as thrombin receptor (PAR-1) antagonists)
- IT **Combinatorial library**
Drug design
Drug screening
Platelet aggregation inhibitors
 (discovery and structure-activity relationships of trisubstituted ureas as thrombin receptor (PAR-1) antagonists)
- IT **Structure-activity relationship (platelet aggregation-inhibiting; discovery and structure-activity relationships of trisubstituted ureas as thrombin receptor (PAR-1) antagonists)**
- IT **Structure-activity relationship (thrombin-inhibiting, thrombin receptor; discovery and structure-activity relationships of trisubstituted ureas as thrombin receptor (PAR-1) antagonists)**
- IT 390405-90-0
 RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
 (discovery and structure-activity relationships of trisubstituted ureas as thrombin receptor (PAR-1) antagonists)
- IT 57-13-6DP, Urea, trisubstituted 147-85-3DP, L-Proline, -derived ureas
 374929-06-3P 374929-08-5P 390404-92-9P 390405-02-4P 390405-06-8P
 390405-16-0P 390405-34-2P 390406-33-4P 390406-68-5P
 RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 (discovery and structure-activity relationships of trisubstituted ureas as thrombin receptor (PAR-1) antagonists)

antagonists)
IT 6287-38-3 6859-99-0, 3-Piperidinol 40499-83-0, 3-Pyrrolidinol
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(discovery and structure-activity relationships of trisubstituted ureas
as thrombin receptor (PAR-1)
antagonists)
IT 52909-94-1P 173086-67-4P 390406-20-9P 390406-53-8P
RL: PKT (Pharmacokinetics); SPN (Synthetic preparation); BIOL (Biological
study); PREP (Preparation)
(discovery and structure-activity relationships of trisubstituted ureas
as thrombin receptor (PAR-1)
antagonists)
IT 374929-07-4P 374929-09-6P 374929-10-9P 374929-11-0P 374929-12-1P
374929-13-2P 374929-18-7P 390405-00-2P 390405-04-6P 390405-08-0P
390405-10-4P 390405-12-6P 390405-14-8P 390405-24-0P 390405-67-1P
390406-05-0P 390406-06-1P 390406-09-4P 390406-13-0P 390406-23-2P
390406-29-8P 390406-31-2P 390406-51-6P 390406-55-0P 390406-57-2P
390406-65-2P 390406-73-2P 390406-77-6P 390406-82-3P 390406-87-8P
390406-90-3P 390406-92-5P 390407-23-5P 390407-30-4P 390407-32-6P
390407-36-0P 390407-42-8P 390407-55-3P 390407-95-1P 390407-99-5P
390408-01-2P 390408-08-9P 390408-09-0P 390408-12-5P
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(discovery and structure-activity relationships of trisubstituted ureas
as thrombin receptor (PAR-1)
antagonists)
IT 104-63-2, N-Benzylethanolamine 105-07-7 147-85-3, L-Proline, reactions
874-42-0 2181-42-2, Trimethylsulfonium iodide 2632-10-2 5973-71-7
6334-18-5 10203-08-4 20555-91-3, 3,4-Dichloro-iodobenzene 20879-18-9
24964-64-5 34036-07-2 71026-66-9 74003-55-7 94838-55-8
94838-59-2 374929-25-6 374929-32-5 390406-08-3 390406-26-5
390406-91-4 390406-94-7 390406-97-0 390406-99-2 390407-01-9
390407-03-1 390407-06-4 390407-09-7 390407-11-1 390407-13-3
390407-15-5 390408-19-2 390408-20-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(discovery and structure-activity relationships of trisubstituted ureas
as thrombin receptor (PAR-1)
antagonists)
IT 1855-36-3P 13692-15-4P 13906-62-2P 52695-39-3P 78982-97-5P
111991-13-0P 115186-37-3P 158397-38-7P 390404-98-5P 390405-95-5P
390405-98-8P 390406-02-7P 390406-28-7P 390406-30-1P 390406-40-3P
390406-43-6P 390406-45-8P 390406-61-8P 390406-71-0P 390406-80-1P
390407-76-8P 390407-80-4P 390407-82-6P 390407-84-8P 390407-86-0P
390407-88-2P 390407-90-6P 390407-92-8P 390408-04-5P 390408-06-7P
390408-07-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(discovery and structure-activity relationships of trisubstituted ureas
as thrombin receptor (PAR-1)
antagonists)
IT 185028-91-5 185028-98-2
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological
study)
(lead structure of PAR-1 antagonists;
discovery and structure-activity relationships of trisubstituted ureas
as thrombin receptor (PAR-1)
antagonists)
IT 141923-41-3
RL: PAC (Pharmacological activity); BIOL (Biological study)
(mimics; discovery and structure-activity relationships of
trisubstituted ureas as thrombin receptor (
PAR-1) antagonists)
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L60 ANSWER 12 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:661483 HCAPLUS

DN 135:216013

ED Entered STN: 10 Sep 2001

TI GPIIb-lipid bond construct and use thereof

IN Ikeda, Yasuo; Saito, Hiroshi; Mukai, Hiromichi; Mori, Yoshiyuki; Murata, Mitsuru

PA Welfide Corporation, Japan

SO PCT Int. Appl., 27 pp.

CODEN: PIXXD2

DT Patent

LA Japanese

IC ICM C07K014-475

ICS A61K038-14; A61K047-34; A61K009-127; A61K047-24; A61K047-26;
A61K047-14; A61K047-28; A61K045-00; A61K049-06; A61K049-04;
A61K049-14; A61K051-08; A61P007-02; A61P007-04; A61P009-00;
A61P029-00; A61K101-02; A61K123-00

CC 63-6 (Pharmaceuticals)

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|----|---|------|----------|-----------------|--------------|
| PI | WO 2001064743 | A1 | 20010907 | WO 2001-JP1635 | 20010302 <-- |
| | W: | | | | |
| | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, | | | | |
| | CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, | | | | |
| | HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, | | | | |
| | LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, | | | | |
| | SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, | | | | |
| | YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 AU 2001036062 A5 20010912 AU 2001-36062 20010302 <--
 EP 1262490 A1 20021204 EP 2001-908262 20010302 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

US 2003113262 A1 20030619 US 2002-220610 20021021 <--

PRAI JP 2000-57449 A 20000302 <--

WO 2001-JP1635 W 20010302

AB Disclosed are a construct wherein a **glycoprotein (GP)**
Ib is bonded to a lipid via a polyalkylene oxide; and a complex (**GPIb** lipid complex) containing this bond construct and a free lipid.
 This **GPIb** lipid complex is expected as widely applicable in
 practice as, for example, a substitute for **platelets**, drugs
 (preventives and remedies for vascular lesion, vascular damage,
 thrombosis, etc.), diagnostics for vWF deficiency, etc., biol. and
 medicinal reagents, and reagents for **screening platelet**
aggregation inhibitors and **antithrombotic**
 agents. Moreover, the **GPIb** lipid complex is highly useful as
 diagnostics or remedies for examining vascular damage or thrombogenic
 sites. Furthermore, the **GPIb** lipid complex is excellent in the
 retention properties in the blood and can exert sustained pharmacol.
 effects. The above-described bond construct is highly valuable as the
 active ingredient of the **GPIb** lipid complex.

ST glycolipoprotein lipid complex liposome blood disorder

IT Glycolipoproteins

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(**GPIb**, complexes; liposomes containing **GPIb**

-polyalkylene oxide-lipid complexes for diagnostic and therapeutic
 agents for blood-related disorders)

IT **Platelet (blood)**

(artificial; liposomes containing **GPIb**-polyalkylene oxide-lipid
 complexes for diagnostic and therapeutic agents for blood-related
 disorders)

IT Polyoxyalkylenes, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(complexes with **GPIb** and lipids; liposomes containing
GPIb-polyalkylene oxide-lipid complexes for diagnostic and
 therapeutic agents for blood-related disorders)

IT Polyoxyalkylenes, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(complexes; with **GPIb** and lipids; liposomes containing
GPIb-polyalkylene oxide-lipid complexes for diagnostic and
 therapeutic agents for blood-related disorders)

IT Fatty acids, biological studies

Glycerides, biological studies

Glycophospholipids

Phospholipids, biological studies

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(complexes, with **GPIb**; liposomes containing **GPIb**

-polyalkylene oxide-lipid complexes for diagnostic and therapeutic
 agents for blood-related disorders)

IT Anti-inflammatory agents

Anticoagulants

Blood vessel, disease

Platelet aggregation inhibitors

Vasoconstrictors

Vasodilators

Von Willebrand's disease

(liposomes containing **GPIb**-polyalkylene oxide-lipid complexes for
 diagnostic and therapeutic agents for blood-related disorders)

IT Drug delivery systems

(liposomes; liposomes containing GPIb-polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

IT 109319-16-6, Von Willebrand's factor

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(liposomes containing GPIb-polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

IT 57-88-5D, Cholesterol, complexes with GPIb and PEG 9003-11-6D, Ethylene oxide-propylene oxide copolymer, complexes with GPIb and lipids 25322-68-3D, Polyethylene glycol, complexes with GPIb and lipids 25322-69-4D, Polypropylene glycol, complexes with GPIb and lipids

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liposomes containing GPIb-polyalkylene oxide-lipid complexes for diagnostic and therapeutic agents for blood-related disorders)

RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

- (1) The Regents Of The University Of California; EP 1078079 A1 HCAPLUS
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L60 ANSWER 13 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:617855 HCAPLUS

DN 135:175384

ED Entered STN: 24 Aug 2001

TI Methods of modulating **protease-activated receptor-4 (PAR4) activation** via cathepsin G

IN Sambrano, Gilberto; Coughlin, Shaun R.

PA The Regents of the University of California, USA

SO PCT Int. Appl., 66 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K038-55

ICS A61K039-395; G01N033-50; C12N015-09; A61K038-06; A61P009-10; A61P029-00; A61P009-00

CC 1-8 (Pharmacology)

Section cross-reference(s): 15

FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| WO 2001060401 | A1 | 20010823 | WO 2001-US4987 | 20010214 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |

PRAI US 2000-506431 A2 20000217

AB The present invention provides methods for modulating cathepsin G-mediated **PAR4 activation** and/or **platelet**

activation. Further, the invention provides methods for **screening agents** which may modulate cathepsin G-mediate **PAR4 activation** and/or **platelet activation.**

- ST protease activated receptor 4**
 cathepsin G modulator; **PAR4 activation** cathepsin G modulator **platelet; platelet activation**
PAR4 cathepsin G modulator
- IT Receptors**
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (PAR-4 (proteinase-activated receptor 4); methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)
- IT Platelet (blood)**
 (activation; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)
- IT Platelet (blood)**
 (aggregation, in cathepsin G-mediated PAR4 activation determination; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)
- IT Heart, disease**
 (angina pectoris, unstable, treatment; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)
- IT Biological transport**
 (calcium, in cathepsin G-mediated PAR4 activation determination; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)
- IT Lung, disease**
 (embolism, treatment; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)
- IT Organ, animal**
 (failure, treatment; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)
- IT Phosphoinositides**
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
 (hydrolysis, in cathepsin G-mediated PAR4 activation determination; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)
- IT Heart, disease**
 (infarction, treatment; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)
- IT Anti-inflammatory agents**
Anticoagulants

Drug delivery systems

Drug screening

Neutrophil

Platelet aggregation inhibitors

(methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)

IT Cell aggregation

(platelet, in cathepsin G-mediated PAR4 activation determination; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)

IT Cell activation

(platelet; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)

IT Brain, disease

(stroke, treatment; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)

IT Antibodies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(to PAR4, cathepsin G-mediated PAR4 activation inhibition by; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)

IT Thrombosis

Transplant and Transplantation

(treatment; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)

IT 59880-97-6

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(cathepsin G release from neutrophils stimulation by; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)

IT 7440-70-2, Calcium, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(in cathepsin G-mediated PAR4 activation determination; methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to effect of neutrophils)

IT 56645-49-9, Cathepsin G

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)

(methods of modulating protease-activated receptor-4 (PAR4) activation via cathepsin G and platelet activation in relation to

effect of neutrophils)
IT 56-65-5, 5'-ATP, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(secretion by **platelets** of, in cathepsin G-mediated
PAR4 activation determination; methods of modulating
protease-activated receptor-4 (
PAR4) **activation** via cathepsin G and **platelet**
activation in relation to effect of neutrophils)
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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(8) Xu; PNAS 1999, V95, P6642

L60 ANSWER 14 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:612021 HCAPLUS
DN 136:548
ED Entered STN: 23 Aug 2001
TI **Thrombin receptor (PAR-1)**
antagonists. Solid-phase synthesis of indole-based peptide
mimetics by anchoring to a secondary amide
AU Zhang, H.-C.; McComsey, D. F.; White, K. B.; Addo, M. F.; Andrade-Gordon,
P.; Derian, C. K.; Oksenberg, D.; Maryanoff, B. E.
CS Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute,
Spring House, PA, 19477-0776, USA
SO Bioorganic & Medicinal Chemistry Letters (2001), 11(16), 2105-2109
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-12 (Pharmacology)
Section cross-reference(s): 34
AB A novel, 10-step, solid-phase method, based on a secondary amide linker,
was developed to construct a diverse library of indole-based SFLLR peptide
mimetics as **thrombin receptor (protease-**
activated receptor 1, PAR-1
) **antagonists**. The key steps include stepwise reductive
alkylation, urea formation, and Mannich reaction. **Screening** of
the library led to a quick development of the SAR and the significant
improvement of **PAR-1** activity.
ST peptidomimetic prepn **thrombin receptor**
antagonist
IT **Receptors**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(**PAR-1 (protease-activated**
receptor 1); solid-phase synthesis of indole-based
peptidomimetic **thrombin receptor (PAR-**
1) antagonists by anchoring to a secondary amide and
structure activity studies)
IT Alkylation
(reductive; solid-phase synthesis of indole-based peptidomimetic
thrombin receptor (PAR-1)
antagonists by anchoring to a secondary amide and structure
activity studies)
IT Mannich reaction
Peptide library

Peptidomimetics

Structure-activity relationship

(solid-phase synthesis of indole-based peptidomimetic **thrombin receptor (PAR-1) antagonists** by anchoring to a secondary amide and structure activity studies)

IT **Thrombin receptors**

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(solid-phase synthesis of indole-based peptidomimetic **thrombin receptor (PAR-1) antagonists** by anchoring to a secondary amide and structure activity studies)

IT 252889-86-4, RWJ-53052

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(solid-phase synthesis of indole-based peptidomimetic **thrombin receptor (PAR-1) antagonists** by anchoring to a secondary amide and structure activity studies)

IT 252889-87-5P 252889-88-6P 316149-51-6P 316149-59-4P 316149-65-2P
 316149-71-0P 316150-31-9P 316150-40-0P 316150-46-6P 316150-75-1P
 316151-44-7P 316151-47-0P 316151-49-2P 375392-69-1P 375392-70-4P
 375392-71-5P 375392-72-6P 375392-73-7P 375392-74-8P 375392-75-9P
 375392-76-0P 375392-77-1P 375392-78-2P 375392-79-3P 375392-80-6P
 375392-81-7P 375392-82-8P 375392-83-9P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)

(solid-phase synthesis of indole-based peptidomimetic **thrombin receptor (PAR-1) antagonists** by anchoring to a secondary amide and structure activity studies)

IT 57-13-6, Urea, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(solid-phase synthesis of indole-based peptidomimetic **thrombin receptor (PAR-1) antagonists** by anchoring to a secondary amide and structure activity studies)

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

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- (1) Ahn, H; Bioorg Med Chem Lett 1999, V9, P2073 HCAPLUS
- (2) Alexopoulos, K; J Med Chem 2001, V44, P328 HCAPLUS
- (3) Andrade-Gordon, P; Proc Natl Acad Sci USA 1999, V96, P12257 HCAPLUS
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L60 ANSWER 15 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2001:455649 HCAPLUS

DN 135:164961

ED Entered STN: 24 Jun 2001

TI Unique pathway of **thrombin-induced platelet aggregation** mediated by **glycoprotein Ib**

AU **Soslau, Gerald**; Class, Reiner; Morgan, Doris A.; Foster, Carolyn; Lord, Susan T.; Marchese, Patrizia; Ruggeri, Zaverio M.

CS Departments of Biochemistry, Medicine, Division of Hematology/Oncology, MCP Hahnemann School of Medicine, Philadelphia, PA, 19102, USA

SO Journal of Biological Chemistry (2001), 276(24), 21173-21183
CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

CC 13-5 (Mammalian Biochemistry)

AB **Thrombin** plays a central role in normal and abnormal hemostatic

processes. It is assumed that α - **thrombin**

activates platelets by hydrolyzing the **protease**

-activated receptor (PAR)-1,

thereby exposing a new N-terminal sequence, a **tethered ligand**,

which initiates a cascade of mol. reactions leading to thrombus formation.

This process involves crosslinking of adjacent **platelets**

mediated by the interaction of **activated glycoprotein**

(GP) IIb/IIIa with distinct amino acid sequences, LGGAKQAGDV

and/or RGD, at each end of dimeric fibrinogen mols. We demonstrate here

the existence of a second α - **thrombin-induced**

platelet-activating pathway, dependent on GP

Ib, which does not require hydrolysis of a substrate

receptor, utilizes polymerizing fibrin instead of fibrinogen, and can

be **inhibited** by the Fab fragment of the monoclonal antibody

LJIB-10 bound to the **GP Ib thrombin-binding**

site or by the cobra venom metalloproteinase, mocarhagin, that hydrolyzes the extracellular portion of **GP Ib**. This alternative

α - **thrombin** pathway is observed when **PAR-1**

or GP IIb/IIIa is **inhibited**. The recognition sites

involved in the crosslinking of polymerizing fibrin and surface integrins via

the **GP Ib** pathway are different from those associated

with fibrinogen. This pathway is insensitive to RGDS and anti-GP

IIb/IIIa antibodies but reactive with a mutant fibrinogen, γ 407,

with a deletion of the γ -chain sequence, AGDV. The reaction is not

due to simple trapping of **platelets** by the fibrin clot, since

ligand binding, signal transduction, and second messenger formation are

required. The **GP Ib** pathway is accompanied by

mobilization of internal calcium and the **platelet** release

reaction. This latter aspect is not observed with ristocetin-induced

GP Ib-von Willebrand factor agglutination nor with

GP Ib-von Willebrand factor polymerizing fibrin trapping of

platelets. Human **platelets** also respond to γ -

thrombin, an autolytic product of α - **thrombin**

, through **PAR-4**. Co-activation of the

GP Ib, PAR-1, and PAR-

4 pathways elicit synergistic responses. The presence of the GP Ib pathway may explain why anti- α -thrombin/anti-platelet regimens fail to completely abrogate thrombosis/restenosis in the cardiac patient.

ST **thrombin fibrin polymn calcium platelet aggregation**

IT Glycolipoproteins

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(GPIb; unique pathway of **thrombin-induced platelet aggregation** mediated by **glycoprotein Ib**)

IT **Platelet (blood)**

(**aggregation**; unique pathway of **thrombin-induced platelet aggregation** mediated by **glycoprotein Ib**)

IT Fibrins

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(in unique pathway of **thrombin-induced platelet aggregation** mediated by **glycoprotein Ib**)

IT **Cell aggregation**

(**platelet**; unique pathway of **thrombin-induced platelet aggregation** mediated by **glycoprotein Ib**)

IT **Molecular association**

(unique pathway of **thrombin-induced platelet aggregation** mediated by **glycoprotein Ib**)

IT 7440-70-2, Calcium, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(release in unique pathway of **thrombin-induced platelet aggregation** mediated by **glycoprotein Ib**)

IT 9002-04-4, **Thrombin**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(unique pathway of **thrombin-induced platelet aggregation** mediated by **glycoprotein Ib**)

RE.CNT 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD

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- L60 ANSWER 16 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:202249 HCAPLUS
ED Entered STN: 22 Mar 2001
TI Discovery of potent, non-peptide **thrombin receptor antagonists**
AU Chackalamannil, Samuel; Xia, Yan; Clasby, Martin; Greenlee, William; Doller, Dario; Eagen, Keith; Tsai, Hsingan; Asberom, Theodros; Lin, Yan; Czarniecki, Michael; Ahn, Ho-Sam; Foster, Carolyn; Boykow, George
CS CV/CNS Chemical Research, Schering-Plough Research Institute, Kenilworth, NJ, 07033, USA
SO Abstracts of Papers - American Chemical Society (2001), 221st, MEDI-342
CODEN: ACSRAL; ISSN: 0065-7727
PB American Chemical Society
DT Journal; Meeting Abstract
LA English
AB In addition to its key role in hemostasis and wound healing, **thrombin activates** specific cell surface **receptors** known as **protease-activated receptors (PAR)**. **Activation of thrombin receptor** stimulates proliferative and proinflammatory processes in a variety of cell types and

may have implications in thrombosis, atherosclerosis, and restenosis. As such, a **thrombin receptor antagonist** may have considerable utility in the treatment of these diseases. Since a **thrombin receptor antagonist** is specific for the cellular actions of **thrombin** and does not interfere with the coagulation cascade, such agents are likely to confer added safety margin with regard to hemorrhagic side effects. Through high throughput **screening**, we have identified 2-iminobenzimidazole derivs. as well as synthetic analogs of the natural product himbacine as **thrombin receptor antagonists**. Systematic SAR studies in these classes of compds. led to **thrombin receptor antagonists** with single digit-nanomolar IC50 values. These compds. **inhibited thrombin** as well as peptide agonist-induced human **platelet aggregation** in a dose-dependent manner.

L60 ANSWER 17 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:202248 HCAPLUS
ED Entered STN: 22 Mar 2001
TI Non-peptidic small molecule **antagonists** of the human **platelet thrombin receptor (PAR-1)**
AU Nantermet, Philippe G.; Selnick, Harold G.; Barrow, James C.; Lundell, George F.; Rittle, Kenneth E.; Glass, Kristen L.; Young, MaryBeth; Pellicore, Janetta M.; Ngo, Phung L.; Freidinger, Roger M.; Prendergast, Kris; Condra, Cindra; Karczewski, Jerzy; Gould, Robert; Connolly, Thomas M.
CS Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SO Abstracts of Papers - American Chemical Society (2001), 221st, MEDI-341
CODEN: ACSRAL; ISSN: 0065-7727
PB American Chemical Society
DT Journal; Meeting Abstract
LA English
AB The synthesis and biol. evaluation of a series of non-peptidic small mol. **antagonists** of the human **platelet thrombin receptor (PAR-1)** are described. The lead 5-amino-3-arylisoxazole was identified by directed **screening** of the Merck sample collection. Optimization of the lead resulted in an approx. 100 fold increase in potency. The most potent of these compds. display IC50s for the **inhibition of platelet activation** in the 100 nM range with the **thrombin receptor** agonist peptide (TRAP) as agonist and also display significant activity when **thrombin** is the agonist.

L60 ANSWER 18 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:796018 HCAPLUS
ED Entered STN: 14 Nov 2000
TI Discovery of a non-peptide small molecule **antagonist** of the human **platelet thrombin receptor (PAR-1)**.
AU Selnick, Harold; Nantermet, Philippe G.; Rittle, Kenneth; Lundell, George F.; Barrow, James C.; Glass, Kristen; Young, Marybeth; Pellicore, Janetta M.; Ngo, Phung L.; Freidinger, Roger; Prendergast, Kris; Gould, Robert; Condra, Cindra; Karczewski, Jerzy; Connolly, Thomas
CS Medicinal Chemistry, Merck Research Laboratories, West Point, PA, 19486, USA
SO Abstracts of Papers - American Chemical Society (2000), 220th, MEDI-021
CODEN: ACSRAL; ISSN: 0065-7727
PB American Chemical Society
DT Journal; Meeting Abstract
LA English
AB Abstract- The synthesis and biol. evaluation of a series of non-peptidic

4/27
small mol. **antagonists** of the human **platelet thrombin receptor (PAR-1)** are described. The lead 5-(N,N-dialkylamino)-3-phenylisoxazole (1) was identified by directed **screening**. Optimization of the lead resulted in an approx. 200 fold increase in potency. The most potent of these compds. display IC50s for the **inhibition** of **platelet activation** in the 0.1 to 1 uM range with the **thrombin receptor** agonist peptide (TRAP, 3uM) as agonist and also display significant activity when **thrombin** (1 nM) is the agonist. Compds. of this class also **inhibit platelet aggregation** stimulated by **thrombin** (1 nM).

L60 ANSWER 19 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:728849 HCAPLUS
DN 132:44502
ED Entered STN: 17 Nov 1999
TI Design, synthesis, and biological characterization of a peptide-mimetic **antagonist** for a **tethered-ligand receptor**
AU Andrade-Gordon, Patricia; Maryanoff, Bruce E.; Derian, Claudia K.; Zhang, Han-Cheng; Addo, Michael F.; Darrow, Andrew L.; Eckardt, Annette J.; Hoekstra, William J.; McComsey, David F.; Oksenberg, Donna; Reynolds, Elwood E.; Santulli, Rosemary J.; Scarborough, Robert M.; Smith, Charles E.; White, Kimberly B.
CS Drug Discovery, The R. W. Johnson Pharmaceutical Research Institute, Spring House, PA, 19477, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1999), 96(22), 12257-12262
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 1-3 (Pharmacology)
AB **Protease-activated receptors (PARs)**
) represent a unique family of seven-transmembrane G protein-coupled **receptors**, which are enzymically cleaved to expose a truncated extracellular N terminus that acts as a **tethered activating** ligand. **PAR-1** is cleaved and **activated** by the serine **protease α -thrombin**, is expressed in various tissues (e.g., **platelets** and vascular cells), and is involved in cellular responses associated with hemostasis, proliferation, and tissue injury. We have discovered a series of potent peptide-mimetic **antagonists** of **PAR-1**, exemplified by RWJ-56110. Spatial relationships between important functional groups of the **PAR-1** agonist peptide epitope SFLLRN were employed to design and synthesize candidate ligands with appropriate groups attached to a rigid mol. scaffold. Prototype RWJ-53052 was identified and optimized via solid-phase parallel synthesis of chemical libraries. RWJ-56110 emerged as a potent, selective **PAR-1 antagonist**, devoid of **PAR-1** agonist and **thrombin inhibitory** activity. It binds to **PAR-1**, interferes with **PAR-1** calcium mobilization and cellular function (**platelet aggregation**; cell proliferation), and has no effect on **PAR-2**, **PAR-3**, or **PAR-4**. By flow cytometry, RWJ-56110 was confirmed as a direct **inhibitor** of **PAR-1 activation** and internalization, without affecting N-terminal cleavage. At high concns. of α - **thrombin**, RWJ-56110 fully **blocked activation** responses in human vascular cells, albeit not in human **platelets**; whereas, at high concns. of SFLLRN-NH2, RWJ-56110 **blocked activation** responses in both cell types. Thus, **thrombin** **activates** human **platelets** independently of **PAR-1**,

i.e., through PAR-4, which we confirmed by PCR anal.

Selective PAR-1 antagonists, such as

RWJ-56110, should serve as useful tools to study PARs and may have therapeutic potential for treating thrombosis and restenosis.

ST peptidomimetic structure thrombin receptor

PAR1 antagonist

IT Thrombin receptors

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(PAR-1 (protease-activated

receptor 1); design, synthesis, and biol.

characterization of peptidomimetic antagonists for

protease-activated receptor PAR-

1)

IT Drug design

Peptidomimetics

Platelet aggregation inhibitors

(design, synthesis, and biol. characterization of peptidomimetic

antagonists for protease-activated

receptor PAR-1)

IT Structure-activity relationship

(receptor-binding; design, synthesis, and biol.

characterization of peptidomimetic antagonists for

protease-activated receptor PAR-

1)

IT 252889-86-4P, RWJ 53052 252889-87-5P, RWJ 54399 252889-88-6P, RWJ 56110 252889-89-7P, RWJ 57269

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); BIOL (Biological study); PREP (Preparation)

(design, synthesis, and biol. characterization of peptidomimetic

antagonists for protease-activated

receptor PAR-1)

RE.CNT 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L60 ANSWER 20 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1999:640986 HCAPLUS

DN 131:283053

ED Entered STN: 08 Oct 1999

TI Human **protease-activated receptor**

PAR4 and its cDNA and pharmaceuticals containing the **PAR4** ligand

IN Xu, Wen-feng; Presnell, Scott R.; Yee, David P.; Foster, Donald C.

PA Zymogenetics, Inc., USA; University of Washington

SO PCT Int. Appl., 85 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C12N015-12

ICS C07K014-705; C07K016-28; A61K038-17

CC 6-3 (General Biochemistry)

Section cross-reference(s): 1, 3, 13

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|---|------|----------|-----------------|----------|
| PI | WO 9950415 | A2 | 19991007 | WO 1999-US7100 | 19990331 |
| | WO 9950415 | A3 | 20000309 | | |
| | W: | | | | |
| | AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, | | | | |
| | DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, | | | | |
| | KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, | | | | |
| | NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, | | | | |
| | UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: | | | | |
| | GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, | | | | |
| | ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, | | | | |
| | CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| | US 6111075 | A | 20000829 | US 1998-53866 | 19980401 |
| | AU 9934591 | A1 | 19991018 | AU 1999-34591 | 19990331 |
| | US 6436400 | B1 | 20020820 | US 2000-479130 | 20000107 |
| | US 2003143218 | A1 | 20030731 | US 2002-187049 | 20020628 |
| PRAI | US 1998-53866 | A | 19980401 | | |
| | WO 1999-US7100 | W | 19990331 | | |
| | US 1999-371333 | A3 | 19990810 | | |
| | US 2000-479130 | A3 | 20000107 | | |
| | US 2000-480720 | B3 | 20000107 | | |

AB The present invention relates to **PAR4**, a novel member of the **protease-activated receptor** family, and DNA encoding it. **PAR4** mediates biol. responses and/or cellular signaling in response to **proteases**. **Protease** cleavage of **PAR4** exposes a **PAR4** extracellular amino terminal portion that serves as a ligand for the **PAR4 receptor**. **PAR4** may be used as a target in drug **screening**, and further used to identify proteinaceous or non-proteinaceous **PAR4** agonists and **antagonists**. The present invention also includes antibodies to the **PAR4** polypeptides. A partial cDNA sequence for **PAR4** was identified in an expressed sequence tag database, and the full-length cDNA clone was then isolated from a lymphoma Daudi

cell cDNA library. The ORF codes for a seven transmembrane domain protein of 385 amino acids with 33% amino acid sequence identity with **PAR1**, **PAR2**, and **PAR3**. A putative **protease** cleavage site (Arg-47/Gly-48) was identified within the extracellular amino terminus. COS cells transiently transfected with **PAR4** resulted in the formation of intracellular inositol triphosphate when treated with either **thrombin** or trypsin. A **PAR4** mutant in which Arg-47 was replaced with Ala did not respond to **thrombin** or trypsin. A hexapeptide (GYPGQV) representing the newly exposed **tethered** ligand from the amino terminus of **PAR4** after proteolysis by **thrombin** activated COS cells transfected with either wild-type or the mutant **PAR4**. Northern blot showed that **PAR4** mRNA was expressed in a number of human tissues, with high levels being present in lung, pancreas, thyroid, testis, and small intestine. By fluorescence in situ hybridization, the human **PAR4** gene was mapped to chromosome 19p12.

ST sequence human **protease activated receptor**

PAR4 cDNA

IT Animal cell line

(Daudi; human **protease-activated receptor**

PAR4 and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT **Receptors**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)

(**PAR-4 (proteinase-activated receptor 4)**; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT

Lung

Pancreas

Testis

Thyroid gland

(**PAR4** gene expression in; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT

cDNA sequences

(for human **protease-activated receptor 4**)

IT

Chromosome

(human 19, **PAR4** gene mapped to; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT

Signal transduction, biological

(human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT

Genetic mapping

(of **PAR4** gene to human chromosome 19p12; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT

Protein sequences

(of human **protease-activated receptor 4**)

IT

Intestine

(small, **PAR4** gene expression in; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing **PAR4** ligand)

IT

mRNA

RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(tissue distribution of **PAR4**; human **protease-**

activated receptor PAR4 and its cDNA and pharmaceuticals containing PAR4 ligand)

IT 225779-44-2
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(PAR4 ligand; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing PAR4 ligand)

IT 98849-88-8 141136-83-6 245652-78-2 245654-44-8 245654-52-8
245654-73-3 245654-80-2
RL: PRP (Properties)
(Unclaimed; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing the PAR4 ligand)

IT 210413-73-3 210413-76-6 210413-81-3
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(amino acid sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing PAR4 ligand)

IT 245113-08-0 245113-09-1 245113-10-4
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing PAR4 ligand)

IT 210527-54-1
RL: PRP (Properties)
(nucleotide sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing PAR4 ligand)

IT 245739-94-0, PN: WO9950415 SEQID: 3 unclaimed DNA 245739-95-1, PN: WO9950415 SEQID: 9 unclaimed DNA 245739-96-2, PN: WO9950415 SEQID: 10 unclaimed DNA 245739-97-3, PN: WO9950415 SEQID: 11 unclaimed DNA 245739-98-4, PN: WO9950415 SEQID: 12 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing the PAR4 ligand)

IT 245750-04-3, PN: WO9950415 SEQID: 5 unclaimed protein
RL: PRP (Properties)
(unclaimed protein sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing the PAR4 ligand)

IT 245740-00-5, PN: WO9950415 PAGE: 6 unclaimed sequence 245740-01-6, PN: WO9950415 PAGE: 6 unclaimed sequence 245740-02-7, PN: WO9950415 PAGE: 6 unclaimed sequence 245740-03-8, PN: WO9950415 PAGE: 6 unclaimed sequence
RL: PRP (Properties)
(unclaimed sequence; human **protease-activated receptor PAR4** and its cDNA and pharmaceuticals containing the PAR4 ligand)

L60 ANSWER 21 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:566175 HCAPLUS
DN 131:181454
ED Entered STN: 08 Sep 1999
TI Nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α -thrombin signaling
IN Coughlin, Shaun R.; Kahn, Mark
PA The Regents of the University of California, USA

SO PCT Int. Appl., 69 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 IC ICM C12N015-12
 ICS C07K014-705; C12N009-74; C07K016-28; C12N001-21; C12N001-19;
 C12N005-10; C12Q001-00; G01N033-68; A61K038-48; A61K038-17
 CC 6-3 (General Biochemistry)
 Section cross-reference(s): 3, 13, 63

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|--|------|----------|-----------------|----------|
| PI | WO 9943809 | A2 | 19990902 | WO 1999-US2983 | 19990211 |
| | WO 9943809 | A3 | 19991014 | | |
| | W: AU, CA, JP, KR, NO | | | | |
| | RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | CA 2321142 | AA | 19990902 | CA 1999-2321142 | 19990211 |
| | AU 9926728 | A1 | 19990915 | AU 1999-26728 | 19990211 |
| | EP 1056854 | A2 | 20001206 | EP 1999-906934 | 19990211 |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| | JP 2002504369 | T2 | 20020212 | JP 2000-533549 | 19990211 |
| | NO 2000004274 | A | 20001013 | NO 2000-4274 | 20000825 |
| PRAI | US 1998-32397 | A | 19980227 | | |
| | WO 1999-US2983 | W | 19990211 | | |

AB Disclosed are cDNAs and genomic DNAs encoding **protease-activated receptor 4 (PAR4)** from mouse and human, and the recombinant polypeptides expressed from such cDNAs. The recombinant **receptor** polypeptides, **receptor** fragments and analogs expressed on the surface of cells are used in methods of **screening** candidate compds. for their ability to act as agonists or **antagonists** to the effects of interaction between **thrombin** and **PAR4**. Agonists are used as therapeutics to treat wounds, promote clotting, and as reagents to **activate platelets** in diagnostic tests. **Antagonists** are used as therapeutics to control blood coagulation, treat heart attack and stroke, and **block** inflammatory and proliferative responses to injury as occur in normal wound healing and variety of diseases including atherosclerosis, restenosis, pulmonary inflammation (ARDS) and glomerulosclerosis. Antibodies specific for a **protease-activated receptor 4** (or **receptor** fragment or analog) and their use as a therapeutic are also disclosed.

ST **protease activated receptor 4** cDNA
 sequence human; **thrombin** signaling **protease activated receptor 4**

IT Drugs
 (agonists/antagonists; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)

IT Antiarteriosclerotics
 (antiatherosclerotics; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)

IT Heart, disease
 (attack, treatment of; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)

IT Molecular cloning
 (expression system; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)

IT **Drug screening**

- (for agonists/antagonists; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT cDNA sequences
(for human and murine **protease-activated receptor PAR-4**)
- IT Lung, disease
(inflammation, treatment of; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT **Anticoagulants**
Coagulants
Wound healing promoters
(nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT Antibodies
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT Protein sequences
(of human and murine **protease-activated receptor PAR-4**)
- IT DNA sequences
(of murine **protease-activated receptor PAR-4** gene intron 1)
- IT **Cell aggregation**
(platelet; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT Artery, disease
(restenosis, treatment of; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT Brain, disease
(stroke, treatment of; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT Megakaryocyte
Spleen
(tissue expression specific for; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT 9002-04-4, **Thrombin** 9002-07-7, Trypsin 164081-25-8
213018-42-9 225779-44-2 239076-98-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(activation by; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT 210413-73-3 213124-64-2
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(amino acid sequence; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT 177872-36-5, GenBank W75830
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(isolation of murine cDNA using; nucleic acids encoding human and

murine **protease-activated receptor**4 and their uses in α - **thrombin** signaling)

- IT 212277-59-3 239124-21-1 239124-23-3
 RL: ANT (Analyte); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
 (nucleotide sequence; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)
- IT 239077-05-5 239077-06-6 239077-07-7 239077-52-2
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
 (peptide **antagonist**; nucleic acids encoding human and murine **protease-activated receptor 4** and their uses in α - **thrombin** signaling)

- 9/27
 L60 ANSWER 22 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 1999:314936 HCAPLUS
 DN 131:124796
 ED Entered STN: 24 May 1999
 TI **Proteinase-activated tethered ligand receptors (PARs): novel targets for drug development**
 AU Hollenberg, Morley D.
 CS Endocrine, Smooth Muscle and Cancer Biology Research Groups Department of Pharmacology & Therapeutics and Department of Medicine University of Calgary, Faculty of Medicine, Calgary, AB, T2N 4N1, Can.
 SO Biomedical and Health Research (1999), 22(Bioactive Peptides in Drug Discovery and Design: Medical Aspects), 265-274
 CODEN: BIHREN; ISSN: 0929-6743
 PB IOS Press
 DT Journal; General Review
 LA English
 CC 1-0 (Pharmacology)
 Section cross-reference(s): 13
 AB A review with 58 refs. The search for the **thrombin receptor** led to the discovery of a **proteinase-activated G-protein-coupled receptor (PAR1)** that is **activated** by a **tethered-ligand** mechanism. Because short peptides based on the **tethered** ligand sequence of **PAR1** can, in isolation, **activate PAR1**, considerable effort has gone into the study of the structure-activity relationships for the **receptor-activating** peptides (**PAR-APs**). Shortly after the description of **PAR1**, two new **proteinase-activated receptors** were discovered, one (**PAR2**) **activated** by trypsin, but not **thrombin**; and another (**PAR3**), **activated** preferentially by **thrombin**. Reports of the discovery of yet another **thrombin-activated receptor (PAR4)** have also been published. The amino acid sequences of the **tethered activating** ligands for the human **receptors** are: SFLLRN...(PAR1); SLIGKV...(PAR2), TFRGAP...(PAR3) and GYPGQV...(PAR4). Structure-activity studies for the differential **activation** of the different **PARs** by these **tethered** ligand sequences has revealed a complex cross-reactivity of the **PAR-APs** for the different **receptors**. Further, pharmacol. data obtained with the **PAR-APs** point to the existence of a more extended **receptor** superfamily for which not all members have yet been cloned. This situation bears directly on the development of **PAR-selective** agonists and **antagonists** that may prove of therapeutic utility.
 ST review **proteinase receptor** drug development target
 IT G protein-coupled **receptors**
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(**PAR (proteinase-activated
receptor); proteinase-activated
tethered ligand receptors (PARs)** as novel
targets for drug development)

IT Structure-activity relationship
(**proteinase-activated receptor-affecting;
proteinase-activated tethered ligand
receptors (PARs)** as novel targets for drug
development)

IT Drug design
Pharmacodynamics
(**proteinase-activated tethered ligand
receptors (PARs)** as novel targets for drug
development)

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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L60 ANSWER 23 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1998:293364 HCAPLUS

DN 129:12725

ED Entered STN: 20 May 1998

TI **Protease-activated receptor 3** and
therapeutic uses thereof

IN Coughlin, Shaun R.; Ishihara, Hiroaki; Connolly, Andrew

PA Regents of the University of California, USA

SO PCT Int. Appl., 74 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-00

ICS A61K035-00; A61K038-00; C07K014-435; C07K014-705; C12N005-10;
C12N015-12; C12N015-63; G01N033-53; G01N033-566

CC 1-1 (Pharmacology)

Section cross-reference(s): 9, 15

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|---|------|----------|-----------------|--------------|
| PI | WO 9818456 | A1 | 19980507 | WO 1997-US19732 | 19971029 <-- |
| | W: CA, JP | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| | US 5892014 | A | 19990406 | US 1996-742440 | 19961030 <-- |
| | EP 948323 | A1 | 19991013 | EP 1997-946388 | 19971029 <-- |
| | R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| | JP 2001510988 | T2 | 20010807 | JP 1998-520768 | 19971029 <-- |
| PRAI | US 1996-742440 | A | 19961030 | <-- | |
| | WO 1997-US19732 | W | 19971029 | <-- | |

AB Disclosed are cDNAs and genomic DNAs encoding **protease-activated receptor 3 (PAR3)** from mouse and human, and the recombinant polypeptides expressed from such cDNAs. The recombinant **receptor** polypeptides, **receptor** fragments and analogs expressed on the surface of cells are used in methods of **screening** candidate compds. for their ability to act as agonists or **antagonists** to the effects of interaction between **thrombin** and **PAR3**. Agonists are used as the therapeutics to treat wounds, thrombosis, atherosclerosis, restenosis, inflammation, and other **thrombin-activated** disorders. **Antagonists** are used as therapeutics to control blood coagulation and thereby treating heart attack and stroke. **Antagonists** mediate inflammatory and proliferative responses to injury as occur in normal wound healing and variety of diseases including atherosclerosis, restenosis, pulmonary inflammation (ARDS) and glomerulosclerosis. Antibodies specific for a **protease-activated receptor 3** (or **receptor** fragment or analog) and their use as a therapeutic are also disclosed.

ST **protease activated receptor 3**
modulator sequence

IT **Receptors**
RL: PRP (Properties)
(**PAR-3** (**proteinase-activated receptor 3**); **protease-activated receptor 3** and therapeutic uses thereof)

IT Drug delivery systems
(carriers; **protease-activated receptor 3** and therapeutic uses thereof)

IT Phosphoinositides
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hydrolysis of; **protease-activated receptor 3** and therapeutic uses thereof)

IT Bioassay
Blood coagulation
DNA sequences
Drug screening
Genetic vectors
Molecular cloning
Platelet aggregation inhibitors

Protein sequences

cDNA sequences

(protease-activated receptor 3
and therapeutic uses thereof)

IT 207754-23-2P 207754-26-5P

RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); USES (Uses)

(amino acid sequence; **protease-activated receptor 3** and therapeutic uses thereof)

IT 207754-21-0P 207754-22-1P 207754-24-3P 207754-25-4P

RL: BOC (Biological occurrence); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation)

(nucleotide sequence; **protease-activated receptor 3** and therapeutic uses thereof)

IT 207461-57-2 207461-58-3 207461-59-4 207461-60-7

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(protease-activated receptor 3
and therapeutic uses thereof)IT 9002-04-4, **Thrombin**RL: BSU (Biological study, unclassified); BIOL (Biological study)
(proteins activated by; **protease-activated receptor 3** and therapeutic uses thereof)RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE

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(2) Coughlin; US 5256766 A 1993 HCAPLUS

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(4) Nystedt; Proc Natl Acad Sci USA 1994, V91, P9208 HCAPLUS

L60 ANSWER 24 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1997:43728 HCAPLUS

DN 126:142434

ED Entered STN: 20 Jan 1997

TI A possible dual physiological role of extracellular ATP in the modulation
of **platelet aggregation**

AU Soslau, Gerald; Youngprapakorn, Donya

CS Department of Biochemistry, Medical College of Pennsylvania and Hahnemann
University, Philadelphia, PA, 19102-1192, USASO Biochimica et Biophysica Acta (1997), 1355(2), 131-140
CODEN: BBACAQ; ISSN: 0006-3002

PB Elsevier

DT Journal

LA English

CC 13-5 (Mammalian Biochemistry)

AB ATP and ADP are simultaneously released from **activated platelets** in equimolar concns. Micromolar concns. of ATP **inhibit platelet aggregation** by both competitive and non-competitive mechanisms. The current studies addressed the question of how **platelets** respond to agonists in the presence of nanomolar and micromolar concns. of ATP and ADP alone or in combination. This is a significant issue since the concentration of ATP+ADP may vary widely within a microenvironment depending upon the source and cause for the release of the nucleotides. ATP (1-10 nM) was found to significantly enhance the thromboxane A2 analog, U44619-, collagen- and **thrombin-induced platelet aggregations**. Conversely, ATP at 1-100 μ M **inhibited** these same reactions. ADP, in general, behaved exactly opposite to ATP. When equal amts. of ATP and ADP were added together the ADP response appeared to predominate. The

observed ATP-induced response was not due to a hydrolytic product as evidenced by an unaltered response to ATP in the presence of adenosine deaminase or the ATP generating system, creatine phosphate plus creatine phosphokinase. Adenosine (1-10 nM), like ADP, **inhibited** agonist-induced **platelet aggregation**. The stimulation of agonist-induced **platelet aggregation** by 1-10 nM extracellular ATP appears to depend upon the phosphorylation of **platelet** membrane ecto proteins. The ATP analog, β -methylene ATP, that is incapable of serving as a phosphate donor for protein kinases, **inhibited** rather than stimulated agonist-induced **platelet aggregation**. The dual response of **platelets** to low and high concns. of extracellular ATP+ADP may play a physiol. role in hemostasis and thrombosis under normal and pathol. conditions.

ST ATP ADP phosphorylation **platelet aggregation**

IT **Platelet** (blood)

(**aggregation**; possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

IT Cell **aggregation**

(**platelet**; possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

IT Phosphorylation, biological

(possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

IT Collagens, biological studies

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

IT 56-65-5, 5'-ATP, biological studies 58-64-0, 5'-ADP, biological studies

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

IT 58-61-7, Adenosine, biological studies 9002-04-4,

Thrombin 56985-40-1, U46619

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(possible dual physiol. role of extracellular ATP in modulation of **platelet aggregation**)

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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4/27 L60 ANSWER 25 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN
 AN 1995:310801 HCAPLUS
 DN 122:122390
 ED Entered STN: 24 Jan 1995
 TI Identification of novel peptide **antagonists** for von Willebrand factor binding to the **platelet glycoprotein Ib receptor** from a phage epitope library
 AU South, Victoria; Searfoss, George H.; French, Stephen; Cheadle, Christopher; Murray, Edward; Howk, Richard; Jaye, Michael; Ricca, George A.
 CS Dep. Molecular Biol., Rhone-Poulenc Rorer Central Res., Collegeville, PA, USA
 SO Thrombosis and Haemostasis (1995), 73(1), 144-50
 CODEN: THHADQ; ISSN: 0340-6245
 PB Schattauer
 DT Journal
 LA English
 CC 1-1 (Pharmacology)
 Section cross-reference(s): 3
 AB The authors have constructed a fusion phage epitope library in the filamentous bacteriophage fuse5. The library was made by inserting a degenerate oligonucleotide which encodes 15 variable amino acids into the NH2-terminal region of the phage gene III protein. This library, containing over 107 different epitope bearing phage, has been used to identify **inhibitors** of the von Willebrand factor (vWF)-**platelet Glycoprotein Ib** interaction. The library was **screened** with a monoclonal antibody (RG46) that recognized the **GPIb** binding domain of vWF (amino acids 445-733). A total of 30 clones falling into 8 classes have been identified that react with the RG46 antibody. Isolates from all 8 classes are pos. by immunoblot anal. The amino acid sequence of the gene III fusion protein from pos. clones showed a strong homol. to the known RG46 epitope. Peptides identified from the **screen** were synthesized and used to demonstrate that some of the synthetic peptides exhibited **inhibitory** activity towards ristocetin induced binding of vWF to the **GPIb receptor**. Thus, the authors have demonstrated that **screening** a fusion phage epitope library with a monoclonal antibody that **inhibits** vWF binding to the **GPIb receptor** can be a useful tool not only for mapping antibody recognizing determinants, but also can serve as a source for identifying novel peptides that are **antagonists** for vWF binding to the **platelet GPIb receptor**.
 ST peptide **antagonist** von Willebrand factor; **glycoprotein** von Willebrand factor binding **antagonist**; epitope library **screening antithrombotic**
 IT Peptides, biological studies
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(identification of novel peptide **antagonists** for von Willebrand factor binding to **platelet glycoprotein Ib receptor** from a phage epitope library)

IT **Anticoagulants and Antithrombotics**

(identification of potential **antithrombotic** peptides by **screening** a fusion phage epitope library with a monoclonal antibody that **inhibits** von Willebrand factor binding)

IT Glycolipoproteins

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**GPIb**, complexes, identification of novel peptide **antagonists** for von Willebrand factor binding to **platelet glycoprotein Ib receptor** from phage epitope library)

IT 160951-87-1 160951-88-2 160951-89-3 160951-90-6 160951-91-7
160951-92-8 160951-93-9 160951-94-0

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(identification of novel peptide **antagonists** for von Willebrand factor binding to **platelet glycoprotein Ib receptor** from a phage epitope library)

IT 109319-16-6

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(identification of novel peptide **antagonists** for von Willebrand factor binding to **platelet glycoprotein Ib receptor** from a phage epitope library)

L60 ANSWER 26 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1993:617409 HCAPLUS

DN 119:217409

ED Entered STN: 27 Nov 1993

TI Analogs of von Willebrand factor-binding peptides of **glycoprotein GPIb.alpha.** and their manufacture for use as **antithrombotics**

IN Ruggeri, Zaverio M.; Ware, Jerry L.

PA Scripps Research Institute, USA

SO PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K037-00

ICS A61K039-00; C07H015-12; C07H017-00; C07K003-00; C07K013-00;
C07K015-00; C07K017-00

CC 1-8 (Pharmacology)

FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------|---|------|--------------|-----------------|--------------|
| PI | WO 9316712 | A1 | 19930902 | WO 1993-US1734 | 19930225 <-- |
| | W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US | | | | |
| | RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG | | | | |
| | AU 9337347 | A1 | 19930913 | AU 1993-37347 | 19930225 <-- |
| PRAI | US 1992-842077 | | 19920226 <-- | | |
| | WO 1993-US1734 | | 19930225 <-- | | |

AB Peptides derived from **glycoprotein GPIb.alpha.**

sequences that interact with von Willebrand factor are prepared for use as **antithrombotics**. These peptides have amino acid substitutions

that increase their affinity for von Willebrand factor. The peptides are manufactured by expression of the coding sequence in an appropriate host. An analog of His1-Ala302 **glycoprotein GPI.alpha.** with Gly-233 was prepared by site-directed mutagenesis of the gene and the protein manufactured by expression in CHO-KI cells. Ristocetin-induced binding of ¹²⁵I-von Willebrand factor to the novel peptide was measured by an enzyme-linked immunofiltration technique using conditioned medium as a source of the **glycoprotein**. The novel peptide showed binding to von Willebrand factor comparable to the wild type at high ristocetin concns. but the analog more efficient binding at low ristocetin concns. Methods for mutagenesis and **screening** for peptides with increased affinity are described.

- ST **glycoprotein GPIb.alpha** analog von Willebrand factor
 IT Blood platelet
 (activation and adhesion inhibitors for,
 glycoprotein GPIb.alpha. fragments and analogs with
 increased binding to von Willebrand factor as)
 IT Gene, animal
 RL: BIOL (Biological study)
 (cDNA, for amino acid-substituted **glycoprotein GPIb**
 α N-terminal fragment, expression in animal cell culture of)
 IT **Anticoagulants and Antithrombotics**
 Blood platelet aggregation inhibitors
 (**glycoprotein GPIb.alpha.** fragments and analogs
 with increased binding to von Willebrand factor as)
 IT Plasmid and Episome
 (pMW1, cDNA for **glycoprotein GPIb.alpha.** on,
 expression in animal cell culture of)
 IT Plasmid and Episome
 (pMW2, cDNA for **glycoprotein GPIb.alpha.** N-terminal
 fragment on, expression in animal cell culture of)
 IT Plasmid and Episome
 (pMW2/G233V, cDNA for amino acid-substituted **glycoprotein**
 GPIb.alpha. N-terminal fragment on, expression in animal cell
 culture of)
 IT Antibodies
 RL: BIOL (Biological study)
 (to **glycoprotein GPIb.alpha.** fragments and analogs
 binding to von Willebrand factor)
 IT Glycolipoproteins
 RL: BIOL (Biological study)
 (**GPIb**, **GPIb.alpha.**, fragments of, analogs of, with
 increased affinity for von Willebrand factor)
 IT 72-18-4, Valine, biological studies
 RL: BIOL (Biological study)
 (amino acid substitution in **glycoprotein GPIb**
 α with, in preparation analogs with increased affinity for von
 Willebrand factor)
 IT 109319-16-6
 RL: BIOL (Biological study)
 (**glycoprotein GPIb.alpha.** fragment analogs with
 increased affinity for)
 IT 56-40-6, Glycine, biological studies 63-68-3, Methionine, biological
 studies
 RL: BIOL (Biological study)
 (substitution in **glycoprotein GPIb.alpha.** of, in
 preparation analogs with increased affinity for von Willebrand factor)

L60 ANSWER 27 OF 27 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1992:443844 HCAPLUS

DN 117:43844

ED Entered STN: 08 Aug 1992

TI The bioluminescent detection of platelet released ATP:

collagen-induced release and potential errors

AU **Soslau, Gerald**; Parker, Janet

CS Med. Sch., Hahnemann Univ., Philadelphia, PA, 19102-1192, USA

SO Thrombosis Research (1992), 66(1), 15-21

CODEN: THBRAA; ISSN: 0049-3848

DT Journal

LA English

CC 9-5 (Biochemical Methods)

Section cross-reference(s): 13

AB The bioluminescent detection of ATP released from **activated platelets** is an important diagnostic and exptl. assay. Potential errors in the interpretation of the data may be introduced due to the lability of luciferin-luciferase and the amount of **platelet** agonist employed. Loss of luciferin-luciferase activity is temperature dependent with a 50% decrease in activity in 1-4 min at 37°. Plasma components do not appear to contribute to the inactivation of the detection system. Due to the significant loss of enzyme activity at variable times, the method of standardizing ATP concns. is crucial for the accurate determination of ATP released from **activated platelets**. A nearly 5-fold error is introduced into the routinely employed assay procedure where the standard ATP concentration is determined 5 min after the addition of agonist. This report demonstrates that the standard ATP concentration must be determined with a sep. **platelet** sample at the same time as the ATP was released from the agonist-induced exptl. **platelet** sample. A second significant error in the assay system may be introduced by the agonist concentration employed even when the final level of **aggregation** is the same. When collagen is employed as the agonist the amount of ATP released appears to depend, in **part**, on the initial intensity of the **aggregation** response and not on collagen type (Type I vs. IV). The corrective procedures described here for the detection of ATP are not likely to change the qual. results of most studies but would significantly alter the quant. results.

ST ATP release **platelet** detn bioluminescence collagen

IT Blood **platelet**
(ATP release from, of human, factors affecting bioluminescent determination of)

IT Collagens, uses
RL: USES (Uses)
(type I, ATP determination following release from human blood **platelets** by bioluminescent assay response to)

IT Collagens, uses
RL: USES (Uses)
(type IV, ATP determination following release from human blood **platelets** by bioluminescent assay response to)

IT 9002-04-4, **Thrombin**
RL: ANST (Analytical study)
(ATP determination following release from human blood **platelets** by bioluminescent assay response to)

IT 56-65-5, 5'-ATP, analysis
RL: ANT (Analyte); ANST (Analytical study)
(determination of, released from human blood **platelet**, factors affecting bioluminescent method for)

IT 2591-17-5, Luciferin 9014-00-0, Luciferase
RL: ANST (Analytical study)
(in ATP determination from human blood **platelets**, factors affecting)

=> => fil biosis

FILE 'BIOSIS' ENTERED AT 07:12:26 ON 09 MAR 2004

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FILE COVERS 1969 TO DATE.
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RECORDS LAST ADDED: 3 March 2004 (20040303/ED)

FILE RELOADED: 19 October 2003.

=> d all tot 165

L65 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 2003:335571 BIOSIS
DN PREV200300335571
TI (Xi)Melagatran Inhibition of Alpha-Thrombin-Gp Ib and Beta-,
Gamma-Thrombin-Par-4 Platelet Aggregation Pathways.
AU Soslau, Gerald [Reprint Author]; Goldenberg, Seth J. [Reprint
Author]; Navas, Edgar [Reprint Author]; Mattsson, Christer [Reprint
Author]; Nylander, Sven [Reprint Author]
CS Biochemistry, Drexel University College of Medicine, Philadelphia, PA, USA
SO Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No.
971. print.
Meeting Info.: 44th Annual Meeting of the American Society of
Hematology. Philadelphia, PA, USA. December 06-10, 2002. American
Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DT Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LA English
ED Entered STN: 23 Jul 2003
Last Updated on STN: 22 Aug 2003
AB Melagatran is the active form of ximelagatran, an oral direct thrombin
inhibitor, which has been shown to interact directly with alpha-thrombin.
Clinical trials have shown ximelagatran to be as efficacious as warfarin
without requiring routine coagulation monitoring. Thrombin plays a major
role in the regulation of hemostasis and thrombosis. Therefore, the
ability to regulate this proteolytic enzyme is of great clinical
significance. Unfortunately, there are multiple active forms of thrombin
that: differentially activate several receptor types; react with a variety
of substrates, and; are differentially sensitive to inhibitors. To date,
no one drug inhibits all thrombin-linked pathways. It is critical to
evaluate each potential antithrombotic drug to determine if it involves
new, overlapping or synergistic inhibitory activities with current drug
therapies. Methods: Preclinical coagulation studies have been extended to
evaluate the in vitro effect of melagatran on alpha-, beta-, and
gamma-thrombin activities with peptide substrates and human
platelet-induced aggregation at the GP Ib, PAR-1 and PAR-4 thrombin
receptors. Alpha-thrombin activates GP Ib and PAR-1, beta- and
gamma-thrombin activate PAR-4. The final melagatran concentration was
varied between 3.75nM to 3.75uM. Results: At 37.5nM and 375nM melagatran
significantly inhibits the alpha-thrombin hydrolysis of a small thrombin
specific peptide substrate while beta- and gamma-thrombin are marginally
affected. Platelets that have been preincubated for 10 min at 37 C with a
final concentration of 3.75nM melagatran became virtually unresponsive to
alpha-, beta- or gamma-thrombin. PAR-1 was not affected since TRAP-1
(SFLLRNP) induced a full platelet aggregation response. GP Ib and PAR-4
thrombin receptors were inhibited by melagatran. This is evidenced by a
lack of aggregatory response to alpha-thrombin with PAR-1 and PAR-4
inactivated platelets while these same inactivated platelet preparations
aggregated fully in the absence of melagatran via the GP Ib pathway. No
response to TRAP-4A (AYPGKF) was observed with platelets preincubated only
with melagatran. The receptor-drug interaction appears to be reversible
since increasing the agonist levels could overcome the inhibition.

Conclusion: Melagatran appears to target thrombin activated pathways not affected by other commonly employed antithrombotics and may be very important in combination therapies.

CC **General biology - Symposia, transactions and proceedings** 00520
 Pathology - Therapy 12512
 Blood - Blood and lymph studies 15002
 Blood - Blood cell studies 15004
 Pharmacology - General 22002
 Pharmacology - Clinical pharmacology 22005
 Pharmacology - Blood and hematopoietic agents 22008
 Pharmacology - Cardiovascular system 22010

IT Major Concepts
 Blood and Lymphatics (Transport and Circulation); Pharmacology

IT Parts, Structures, & Systems of Organisms
 platelet: blood and lymphatics, aggregation

IT Chemicals & Biochemicals
 (Xi)mela^gatran: antithrombotic-drug, cardiovascular-drug, hematologic-drug; PAR-1 [protease-activated receptor-1]: regulation; PAR-4 [protease-activated receptor-4]: regulation; TRAP-1 [thrombin receptor activating peptide for protease-activated receptor-1]; alpha-thrombin; alpha-thrombin-Gp Ib: regulation; beta-thrombin; gamma-thrombin

IT Miscellaneous Descriptors
 drug synergistic inhibitory activity

ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 human (common)
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 192939-46-1 ((Xi)mela^gatran)
 9002-04-4 (alpha-thrombin)
 9002-04-4 (beta-thrombin)
 9002-04-4 (gamma-thrombin)

L65 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2003:335570 BIOSIS
 DN PREV200300335570
 TI Differential Activation and Inhibition of Human Platelet Thrombin Receptors by Structurally Distinct Alpha-, Beta- and Gamma-Thrombins.
 AU Soslau, Gerald [Reprint Author]; Goldenberg, Seth J. [Reprint Author]; Class, Reiner [Reprint Author]; Jameson, Bradford [Reprint Author]
 CS Biochemistry, Drexel Univ Coll of Medicine, Phila, PA, USA
 SO Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 970. print.
 Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
 CODEN: BLOOAW. ISSN: 0006-4971.

DT **Conference; (Meeting)**
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)

LA English
 ED Entered STN: 23 Jul 2003
 Last Updated on STN: 22 Aug 2003

AB The development of drugs to neutralize the action of thrombin has to date focused on the alpha form of the protease. It is generally agreed that inactive prothrombin is proteolytically converted to active alpha-thrombin which may be further hydrolyzed to beta- and gamma-thrombin. While all three forms of the enzyme retain catalytic activities only alpha-thrombin

is presumed to be physiologically important. The beta- and gamma-thrombin are presumed to be degradation products of no physiological significance. Our demonstration that beta- and gamma-thrombin selectively activate PAR-4 in this and a previous report (J. Biol. Chemical 276, 21173-21183, 2001) necessitates a reevaluation of how we view their physiological role and how we approach the pharmacological regulation of their actions. beta-Thrombin, like gamma-thrombin, at nM levels selectively activates PAR-4. This was demonstrated by full retention of aggregatory activity with platelets whose PAR-1 and GP Ib receptors were inactivated. Furthermore, the beta-thrombin response was abrogated by desensitizing platelets with suboptimal levels of the thrombin receptor activating peptide for PAR-4 (TRAP-4). alpha-Thrombin is rapidly converted to beta- and gamma-thrombin by activated factor X at physiological pH, in vitro. This implies that the same may hold true in vivo in the proper microenvironment. The differential activation of the three platelet thrombin receptors by alpha-, beta- and gamma-thrombin implies selective structural variations between these thrombin species. This would also account for the marked differential response to the antithrombotics, heparin and hirudin, which are found to be poor inhibitors of beta- and gamma-thrombin-induced platelet aggregation. Histone-1 selectively inhibits beta- and gamma-thrombin with no effect on alpha-thrombin. However, histone-1 appears to function primarily at the receptor level of PAR-4 rather than on the thrombin molecule. Since trypsin, like beta- and gamma-thrombin, activates PAR-4 and is also inactive with TRAP-4 desensitized platelets it was hypothesized that the crystalline structure of gamma-thrombin would be more like that of trypsin than alpha-thrombin. The analysis of the crystalline structures of alpha-, gamma-thrombin and trypsin confirm that this is the case. It is further postulated that the physiologic activator of PAR-2 may be beta- and gamma-thrombin since it, like PAR-4, can be activated by trypsin. These findings should help to elucidate structure-function relationships of the different thrombins and may aid in the development of new antithrombotic drugs.

CC **General biology - Symposia, transactions and proceedings 00520**

Biochemistry studies - Carbohydrates 10068

Enzymes - General and comparative studies: coenzymes 10802

Pathology - Therapy 12512

Blood - Blood and lymph studies 15002

Blood - Blood cell studies 15004

Pharmacology - General 22002

Pharmacology - Blood and hematopoietic agents 22008

Pharmacology - Cardiovascular system 22010

IT Major Concepts

Blood and Lymphatics (Transport and Circulation); Pharmacology

IT Parts, Structures, & Systems of Organisms

platelet: blood and lymphatics, aggregatory activity

IT Chemicals & Biochemicals

GP Ib receptor [glycoprotein Ib receptor]: regulation; PAR-1 [protease-activated receptor-1]: regulation; PAR-4 [protease-activated receptor-4]: regulation; alpha-thrombin: catalytic activity, structural variation; beta-thrombin: catalytic activity, structural variation; factor X: regulation; gamma-thrombin: catalytic activity, structural variation; heparin: antithrombotic-drug, cardiovascular-drug, hematologic-drug; hirudin: antithrombotic-drug, cardiovascular-drug, hematologic-drug; histone-1; thrombin receptor: regulation; thrombin receptor activating peptide for protease-activated receptor-4 [TRAP-4]; trypsin [EC 3.4.21.4]: crystalline structure

IT Miscellaneous Descriptors

structure-function relationship

RN 9002-04-4 (alpha-thrombin)

9002-04-4 (beta-thrombin)

9001-29-0 (factor X)

9002-04-4 (gamma-thrombin)

9005-49-6 (heparin)

8001-27-2 (hirudin)
 9002-07-7 (trypsin)
 9002-07-7 (EC 3.4.21.4)

L65 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2001:255186 BIOSIS
 DN PREV200100255186
 TI The three thrombin receptors on human platelets respond differentially to
 alpha-, beta-, and gamma-thrombin.
 AU Soslau, Gerald [Reprint author]; Goldenberg, Seth J. [Reprint
 author]; Class, Reiner [Reprint author]
 CS MCPHahnemann Univ, 245 N 15th Street, Philadelphia, PA, 19102-1192, USA
 SO FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A896. print.
 Meeting Info.: **Annual Meeting of the Federation of American Societies
 for Experimental Biology on Experimental Biology 2001.** Orlando,
 Florida, USA. March 31-April 04, 2001.
 CODEN: FAJOEC. ISSN: 0892-6638.
 DT **Conference; (Meeting)**
Conference; Abstract; (Meeting Abstract)
 LA English
 ED Entered STN: 23 May 2001
 Last Updated on STN: 19 Feb 2002
 AB Cardiovascular diseases remain the leading cause of death in the USA
 despite the availability of clinically employed anti-thrombotic and
 anti-platelet drugs. The presumption that alpha-thrombin and the platelet
 fibrinogen receptor, GP IIb/IIIa, are the two targets in coagulation and
 platelet aggregation pathways that need to be inhibited to fully regulate
 hemostasis and thrombosis needs to be revisited. We have found that the
 controversially defined thrombin receptor, GP Ib, is activated by
 alpha-thrombin via a pathway that is insensitive to GP IIb/IIIa
 inhibitors. The GP Ib pathway is readily detected when PAR-1 is blocked.
 Aggregation under these conditions is inhibited by the anti-GP Ib
 antibody, LJ Ib-10, or by the cobra venom metalloproteinase, mocarhagin,
 that hydrolyzes off the extracellular portion of GP Ib. Furthermore,
 three active forms of thrombin exist with alpha-thrombin being the major
 player, however, the two actoproteolytic products, beta- and
 gamma-thrombin are potentially significant contributors to hemostasis as
 well. These three thrombins function differentially at the three platelet
 thrombin receptors, GP Ib, PAR-1 and PAR-4, and also respond differently
 to thrombin inhibitors. At 0.1-10nM levels of thrombins, PAR-4 can only
 be activated by gamma-thrombin while GP Ib and PAR-1 are insensitive to
 gamma-thrombin, but both respond to alpha-thrombin. Beta-thrombin appears
 to be more selective for PAR-1. Gamma-thrombin/PAR-4 is inhibited
 stoichiometrically by histone-1 while alpha- and beta-thrombins and their
 receptors are insensitive. The three thrombin species display different
 sensitivities to heparin. Gamma-thrombin is totally insensitive to
 hirudin while alpha- and beta-thrombins are completely inhibited. These
 thrombin species can function synergistically and some individuals also
 appear to possess varying levels of the three thrombin receptors. It is
 likely that these disparate properties along with differential responses
 to drugs could account for continued coronary disease processes even in
 the light of aggressive therapy regimens.
 CC Blood - Blood and lymph studies 15002
General biology - Symposia, transactions and proceedings 00520
 Cardiovascular system - Blood vessel pathology 14508
 Blood - Blood cell studies 15004
 IT Major Concepts
 Blood and Lymphatics (Transport and Circulation)
 IT Parts, Structures, & Systems of Organisms
 platelet: blood and lymphatics
 IT Diseases
 cardiovascular disease: vascular disease
 Cardiovascular Diseases (MeSH)

IT Diseases
thrombosis: vascular disease
Thrombosis (MeSH)

IT Chemicals & Biochemicals
LJ Ib-10: anti-GP Ib antibody inhibitor; alpha-thrombin; beta-thrombin;
gamma-thrombin; mocoarhagin: anti-GP Ib antibody inhibitor, cobra venom
metalloproteinase; thrombin receptors

IT Miscellaneous Descriptors
hemostasis; **Meeting Abstract**

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals; Chordates, Humans, Mammals, Primates, Vertebrates

RN 171040-76-9 (mocoarhagin)

L65 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1998:67560 BIOSIS
DN PREV199800067560
TI Aggregation of human platelets and megakaryocyte-like cells (HU3) induced
by a non-RGDS fibrin, non-proteolytic thrombin-GPIb pathway.
AU Soslau, G. [Reprint author]; Morgan, D. A.; Class, R.; Brodsky,
I.; Marchese, P.; Ruggeri, Z. M.
CS Allegheny Univ. Health Sci., Philadelphia, PA, USA
SO Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 284A. print.
Meeting Info.: **39th Annual Meeting of the American Society of
Hematology**. San Diego, California, USA. December 5-9, 1997. The
American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.

DT **Conference; (Meeting)**
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LA English
ED Entered STN: 30 Jan 1998
Last Updated on STN: 30 Jan 1998
CC Blood - General and methods 15001
Cytology - General 02502
Biochemistry studies - General 10060
Cardiovascular system - General and methods 14501
General biology - Symposia, transactions and proceedings 00520

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cardiovascular System
(Transport and Circulation); Cell Biology

IT Parts, Structures, & Systems of Organisms
platelet: blood and lymphatics, aggregation

IT Diseases
atherosclerosis: vascular disease
Arteriosclerosis (MeSH)

IT Chemicals & Biochemicals
fibrin: non-RGDS; fibrinogen; hirudin; thrombin; thrombin-GPIb
[thrombin-glycoprotein Ib]: pathway; SFLLRNP: thrombin receptor
activating peptide; 7 transmembrane thrombin receptor [7TMTR]

IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster

ORGN Classifier
Animalia 33000
Super Taxa
Animalia
Organism Name
HU3: megakaryocyte-like cells

Taxa Notes
 Animals
 ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 human
 Taxa Notes
 Animals; Chordates, Humans, Mammals, Primates, Vertebrates
 RN 8001-27-2 (hirudin)
 9002-04-4 (thrombin)

L65 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 1997:53080 BIOSIS
 DN PREV199799352283
 TI GPIb is a slow response thrombin receptor detectable in human platelets
 and cultured cells independent of a rapid thrombin response.
 AU Soslau, G.; Morgan, D. A.; Brodsky, I.; Class, R.
 CS Allegheny Univ. Health Sci., Philadelphia, PA, USA
 SO Blood, (1996) Vol. 88, No. 10 SUPPL. 1 PART 1-2, pp. 25A.
 Meeting Info.: **Thirty-eighth Annual Meeting of the American Society
 of Hematology**. Orlando, Florida, USA. December 6-10, 1996.
 CODEN: BLOOAW. ISSN: 0006-4971.
 DT Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 Conference; (Meeting Poster)
 LA English
 ED Entered STN: 4 Feb 1997
 Last Updated on STN: 5 Feb 1997
 CC General biology - Symposia, transactions and proceedings 00520
 Cytology - Human 02508
 Biochemistry studies - Proteins, peptides and amino acids 10064
 Biophysics - Membrane phenomena 10508
 Enzymes - Physiological studies 10808
 Blood - Blood and lymph studies 15002
 Blood - Blood cell studies 15004
 In vitro cellular and subcellular studies 32600
 IT Major Concepts
 Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport
 and Circulation); Cell Biology; Enzymology (Biochemistry and Molecular
 Biophysics); Membranes (Cell Biology)
 IT Chemicals & Biochemicals
 THROMBIN
 IT Miscellaneous Descriptors
 BLOOD AND LYMPHATICS; GPIB PROTEIN; HEMOSTASIS; HU3 CELL LINE; PLATELET
 ACTIVATION; RAPID RESPONSE; SLOW RESPONSE THROMBIN RECEPTOR; THROMBIN;
 THROMBOSIS
 ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 human
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates
 RN 9002-04-4 (THROMBIN)

L65 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 1996:51314 BIOSIS
 DN PREV199698623449
 TI Typical and atypical platelet-like responses to thrombin and ATP by HU3, a
 human megakaryocytic (MEG) cell line.

AU Soslau, G. [Reprint author]; Morgan, D. A.; Brodsky, I.
CS Med. Coll. of Pa., Philadelphia, PA, USA
SO Blood, (1995) Vol. 86, No. 10 SUPPL. 1, pp. 909A.
Meeting Info.: 37th Annual Meeting of the American Society of Hematology. Seattle, Washington, USA. December 1-5, 1995.
CODEN: BLOOAW. ISSN: 0006-4971.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LA English
ED Entered STN: 2 Feb 1996
Last Updated on STN: 3 Feb 1996

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Human 02508
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Biochemistry studies - Proteins, peptides and amino acids 10064
Biochemistry studies - Minerals 10069
Enzymes - Physiological studies 10808
Blood - Blood and lymph studies 15002
Blood - Blood cell studies 15004
Blood - Lymphatic tissue and reticuloendothelial system 15008

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology;
Enzymology (Biochemistry and Molecular Biophysics)

IT Chemicals & Biochemicals
THROMBIN; ATP; CALCIUM

IT Miscellaneous Descriptors
CALCIUM; FIBRINOGEN; MEETING ABSTRACT; PLATELET AGGREGATION

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
Hominidae
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

RN 9002-04-4 (THROMBIN)
56-65-5Q (ATP)
42530-29-0Q (ATP)
94587-45-8Q (ATP)
111839-44-2Q (ATP)
7440-70-2 (CALCIUM)

L65 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1995:55622 BIOSIS
DN PREV199598069922
TI Extracellular ATP inhibits agonist-induced mobilization of internal calcium in human platelets.

AU Soslau, Gerald; McKenzie, Robert J.; Brodsky, Isadore; Devlin, Thomas M.
CS Hahnemann Univ., Dep. Biochem., Broad and Vine Sts., Philadelphia, PA, USA
SO Blood, (1994) Vol. 84, No. 10 SUPPL. 1, pp. 322A.
Meeting Info.: Abstracts Submitted to the 36th Annual Meeting of the American Society of Hematology. Nashville, Tennessee, USA. December 2-6, 1994.
CODEN: BLOOAW. ISSN: 0006-4971.

DT Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)

LA English
ED Entered STN: 31 Jan 1995
Last Updated on STN: 1 Feb 1995

CC General biology - Symposia, transactions and proceedings 00520
Cytology - Human 02508

Biochemistry studies - General 10060
 Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
 Metabolism - Minerals 13010
 Blood - Blood cell studies 15004
 Endocrine - Neuroendocrinology 17020
 Nervous system - Physiology and biochemistry 20504
 IT Major Concepts
 Blood and Lymphatics (Transport and Circulation); Endocrine System
 (Cheical Coordination and Homeostasis); Metabolism; Nervous System
 (Neural Coordination)
 IT Chemicals & Biochemicals
 ATP; CALCIUM; UTP; CTP; U-46619
 IT Miscellaneous Descriptors
 ATP ANALOGUES; CTP; **MEETING ABSTRACT; MEETING POSTER**
 ; PURINERGIC RECEPTORS; U-46619; UTP
 ORGN Classifier
 Hominidae 86215
 Super Taxa
 Primates; Mammalia; Vertebrata; Chordata; Animalia
 Organism Name
 human
 Taxa Notes
 Animals, Chordates, Humans, Mammals, Primates, Vertebrates
 RN 56-65-5Q (ATP)
 42530-29-0Q (ATP)
 94587-45-8Q (ATP)
 111839-44-2Q (ATP)
 7440-70-2 (CALCIUM)
 63-39-8 (UTP)
 65-47-4Q (CTP)
 103335-28-0Q (CTP)
 216768-11-5Q (CTP)
 56985-40-1 (U-46619)
 87805-51-4Q (ATP)

=> => fil wpix

FILE 'WPIX' ENTERED AT 07:41:09 ON 09 MAR 2004
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FILE LAST UPDATED: 5 MAR 2004 <20040305/UP>
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=> d all abeq tech abex tot

L84 ANSWER 1 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2004-156422 [15] WPIX

DNN N2004-125194 DNC C2004-062099

TI New modified **PAR** polypeptide, comprising non-functional endogenous **activating** peptide and interacting with an exogenous ligand for a wild-type **PAR receptor** useful for selecting compounds that modulate the activity of **PAR receptor**.

DC B04 D16 S03

IN BERTHELIER, C; BIGOGNE, C; MILANO, S; NORMANT, E

PA (PFIZ) PFIZER INC

CYC 105

PI WO 2004003202 A1 20040108 (200415)* EN 120p C12N015-12

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH
PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC
VN YU ZA ZM ZW

FR 2841559 A1 20040102 (200415) C07K014-705

ADT WO 2004003202 A1 WO 2003-EP6822 20030627; FR 2841559 A1 FR 2002-8173
20020628

PRAI FR 2002-8173 20020628

IC ICM C07K014-705; C12N015-12

ICS C12N005-10; C12N015-63; C12Q001-02; G01N033-50; G01N033-566;
G01N033-68

AB WO2004003202 A UPAB: 20040302

NOVELTY - A modified **PAR** polypeptide, comprising its endogenous **activating** peptide made non-functional and being capable of interacting with an exogenous ligand for a wild-type **PAR receptor**, where the exogenous ligand has an ED50 for the modified **PAR** polypeptide significantly higher than its ED50 for a wild type **PAR receptor**, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

- (1) a polynucleotide encoding the polypeptide;
- (2) an expression vector comprising the polynucleotide;
- (3) a recombinant host cell comprising the polynucleotide;
- (4) preparing a modified **PAR** polypeptide comprising

obtaining a polynucleotide encoding the modified **PAR** polypeptide; inserting the polynucleotide into an expression vector that is functionally linked to a promoter; and producing the modified **PAR** polypeptide from the polynucleotide;

- (5) screening for, selecting or identifying **PAR** activity modulator compounds comprising bringing a test compound into contact with a modified **PAR** polypeptide; and selecting the compounds that bind to the modified **PAR** polypeptide or determining the activity of the modified **PAR** polypeptide; and

- (6) a kit for the in vitro screening, selection or identifying of **PAR** activity modulator compounds comprising the polypeptide, or recombinant host cell, and optionally, the reagents necessary to perform the **PAR** polypeptide activity measurement.

ACTIVITY - Antiinflammatory; Antiallergic; CNS-Gen.; Cardiovascular-Gen.; Neuroleptic. No biological data given.

MECHANISM OF ACTION - None given.

USE - The polypeptide is useful for selecting compounds that modulate the activity of at least one **PAR receptor**. The kit is useful for the in vitro screening, selection or identifying of **PAR** activity modulator compounds (all claimed). The compounds identified are useful for treating inflammation, allergies, diseases affecting the CNS, psychiatric or cardiovascular diseases.

Dwg.0/6

FS CPI EPI

FA AB

MC CPI: B04-E02D; B04-E08; B04-F0100E; B04-K0100E; B11-C08F; B11-C10;
B12-K04E; B14-C03; B14-F01; B14-F02; B14-G02A; B14-J01;
 D05-C12; **D05-H09**; D05-H12B; D05-H12E; D05-H14; D05-H17B4

EPI: S03-E13D; S03-E14H

TECH UPTX: 20040302

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Polypeptide: The modified **PAR** polypeptide comprises an exogenous ligand having an ED50 for the polypeptide at least 5, 10 or 50 times higher than its ED50 for a wild-type **PAR receptor**. The region that extends from the first N-terminal residue of the **PAR** polypeptide up to a residue between the first N-terminal residue of the endogenous **activating** peptide and the last C-terminal residue of the amino-terminal extracellular domain is deleted. The **PAR receptor** is chosen from **PAR-1**, **PAR-2**, **PAR-3** and **PAR-4**. The

polypeptide comprises a sequence of 355, 341 or 320 amino acids fully defined in the specification. The polynucleotide comprises a sequence of 1068, 1026, or 963 bp, fully defined in the specification. It comprises a sequence that differs from those cited above due to the degeneracy of the genetic code.

Preferred Cell: The host cell does not express any wild-type **PAR receptor**. The recombinant host cell also expresses a reporter gene for detecting or measuring the activity of the modified **PAR** polypeptide.

Preferred Method: The screening method comprises bringing a test compound into contact with the **PAR** polypeptide; and selecting the compounds that bind to the modified **PAR** polypeptide or determining the activity of the modified **PAR** polypeptide.

This method comprises:

- (a) providing a recombinant host cell expressing the modified **PAR** polypeptide in an appropriate culture medium;
 - (b) adding a desired concentration of a test compound in the culture medium;
 - (c) adding a reference ligand in the culture medium;
 - (d) measuring the activity of the modified **PAR** polypeptide; and
 - (e) comparing the activity of the modified **PAR** polypeptide obtained with the its activity when the adding step is omitted.
- The modified **PAR** polypeptide activity is measured through calcium release measurement. The **PAR** polypeptide activity measure is direct.

The method alternatively comprises:

- (a) providing a recombinant host cell co-expressing a modified **PAR** polypeptide and a reporter gene;
- (b) adding a desired concentration of a test compound in the culture medium;
- (c) adding a reference ligand in the culture medium;
- (d) measuring the reporter gene expression; and
- (e) comparing the reporter gene expression obtained with the reporter gene expression when the adding step is omitted.

The recombinant host cell consists of a CHO (Chinese hamster ovary) cell line. The reporter gene is a beta-lactamase gene, which is placed under the control of a promoter comprising an NFAT domain sensitive to Ca²⁺ ions. The modified **PAR** polypeptide is a modified **PAR-2** polypeptide. The reference ligand is selected from Ser-Leu-Ile-Gly-Arg-Leu, Ser-Leu-Ile-Gly-Lys-Val, Ser-Leu-Ile-Gly-Arg, propionyl-tc, trans-cinnamoyl-Leu-Ile-Gly-Arg-Leu-O and Ser-Phe-Leu-Leu-Arg.

DNC C2003-237480

TI Treatment of angiogenesis-associated diseases comprises administering composition comprising **Protease-Activated Receptor (PAR)** agonist, e.g. monoclonal antibody, capable of binding directly to the **PAR receptor**.

DC B04 D16

IN CHAN, B; MERCHAN, J; SUKHATME, V P

PA (BETH-N) BETH ISRAEL DEACONESS MEDICAL CENT

CYC 103

PI WO 2003079978 A2 20031002 (200378)* EN 77p A61K000-00

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL
PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU
ZA ZM ZW

ADT WO 2003079978 A2 WO 2003-US8121 20030314

PRAI US 2002-365165P 20020318

IC ICM A61K000-00

AB WO2003079978 A UPAB: 20031203

NOVELTY - Treating angiogenesis-associated diseases, comprising administering a pharmaceutical composition comprising a **Protease-Activated Receptor (PAR)** agonist, where the agonist is capable of binding directly to the **PAR receptor**, is new.

DETAILED DESCRIPTION - Treating (M1) angiogenesis-associated diseases, comprising:

(a) administering a pharmaceutical composition comprising a **Protease-Activated Receptor (PAR)** agonist, where the agonist is capable of binding directly to the **PAR receptor**;

(b) administering a compound which results in **activation of a protease-Activated Receptor (PAR)**), where the treatment does not comprise administering either tissue plasminogen **activator (tPA)** polypeptide or a urokinase plasminogen **activator (uPA)**, where the uPA is capable of binding to the human uPA **receptor (uPA-R)** in combination with captopril;

(c) administering a pharmaceutical composition comprising **thrombin** or **prothrombin** to a patient diagnosed with an angiogenesis associated disease;

(d) administering a pharmaceutical composition comprising a compound that modulates **PAR** biological activity, where the treatment does not comprise administering either tPA polypeptide or a uPA, where the uPA is capable of binding to the human uPA-R if the treatment also comprises administering captopril;

(e) administering a pharmaceutical composition comprising substantially pure urokinase (uPA) polypeptide, where the polypeptide is incapable of binding to the urokinase **receptor**, uPA-R;

(f) introducing a transgene encoding a uPA polypeptide, where the uPA polypeptide is incapable of binding to uPA-R, to a cell, the transgene is operably linked to expression control sequences, and the transgene being positioned for expression in the cell; or

(g) introducing a transgene encoding a **PAR** polypeptide, the transgene is operably linked to expression control sequences, and the transgene being positioned for expression in the cell.

INDEPENDENT CLAIMS are also included for:

(1) a pharmaceutical composition (I) comprising substantially pure **PAR-agonist**, where the agonist is capable of binding directly to the **PAR receptor**;

(2) a pharmaceutical composition (II) comprising a compound which results in **activation of PAR receptor**, where the composition does not comprise either tPA polypeptide or uPA, where the

uPA is capable of binding to the human uPA **receptor**;

(3) identifying (M2) candidate compounds that modulate **PAR** biological activity, comprising contacting the **PAR** to a candidate compound, and measuring binding of the compound to the **PAR receptor**; and

(4) identifying (M3) antiangiogenic molecules in serum plasma, comprising contacting the serum plasma with a tissue **protease** and an ACE inhibitor, depleting the plasma of angiostatin, chromatographically separating plasma fractions, and determining angiogenic potential of the fraction, where inhibition of angiogenesis identifies the fraction as antiangiogenic.

ACTIVITY - Cytostatic; Antirheumatic; Antipsoriatic; Cytostatic; Anti-HIV; Antidiabetic; Ophthalmological; Vulnerary. No biological data given.

MECHANISM OF ACTION - Inhibitor of angiogenesis; Gene Therapy. No biological data given.

USE - (M1) is useful for treating angiogenesis-associated diseases chosen from cancer, rheumatoid arthritis, psoriasis, pyogenic granuloma, HIV Kaposi's sarcoma, diabetic retinopathy, muscular degeneration, corneal graft neovascularization, and hypertrophic scarring. In (M1), the angiogenesis-associated disease is preferably cancer. (M1) further comprises administering antiproliferative agent simultaneously or within 14 days of each other in amounts sufficient to inhibit the growth of the neoplasm. A pharmaceutical composition (I) comprising substantially pure **PAR-agonist** (I) or a pharmaceutical composition (II) comprising a compound which results in **activation of PAR receptor** (II) is useful for the treatment of an angiogenesis associated disease. The angiogenesis associated disease is cancer. The cancer is breast cancer. (I) or (II) further comprises a second therapeutic agent. The second therapeutic agent is an antiproliferative agent (all claimed).

DESCRIPTION OF DRAWING(S) - The figure shows bar graph showing the effects of tissue **protease** overexpression on tumor cell growth.

Dwg.15/15

FS CPI

FA AB; GI; DCN

MC CPI: B04-B04D4; B04-E08; B04-G01; B04-G21; **B04-H19**; B04-L01;
B05-B01E; B06-D01; B06-D03; B06-D04; B07-D03; B11-C10;
B12-K04E; B14-C09B; B14-H01; B14-N03; B14-N17B; B14-N17C;
B14-S03A; B14-S04; **D05-H09**; D05-H11A

TECH UPTX: 20031203

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred **Receptor**: In (M1), the **PAR** is chosen from **PAR-1**, **PAR-3**, and **PAR-4**.

Preferred Agonist: The **PAR-agonist** or **activator** of the **PAR receptor** is chosen from polypeptides such as (P1)-(P5).

Ser-Phe-Leu-Leu-Arg-Asn-Pro-Asn-Asp-Lys-Tyr-Glu-Pro-Phe (P1)

Ser-Phe-Leu-Leu-Arg-Asn (P2)

Ser-Ala-Leu-Leu-Arg-Asn (P3)

Gly-Tyr-Pro-Gly-Lys-Phe (P4)

Ser-Leu-Ile-Gly-Lys-Val (P5)

The **PAR-agonist** is a monoclonal antibody. The monoclonal antibody modulates **PAR-receptor** signaling. The monoclonal antibody further prevents **receptor** internalization.

Preferred Method: (M1) further comprises administering an anti-coagulant.

(M1) further comprises administering an ACE inhibitor which is chosen from captopril, enalapril, lisinopril, benazepril, fosinopril, ramipril, quinapril, perindopril, trandolapril, and moexipril. The serum plasma is mammalian serum plasma. The tissue **protease** is chosen from urokinase, tissue plasminogen **activator**, and streptokinase. In

(M1) the fraction having antiangiogenic activity is further purified to allow for identification. The uPA is mouse, rat, or human. Preferably, uPA

is human uPA. The human uPA further comprises amino acid substitutions within the OMEGA-loop. The OMEGA-loop comprises amino acid residue substitutions on the amino acid sequences chosen from Tyr24-Phe25-Ser26-Asn27-Ile28-His29-Trp30 in human, Tyr24-Phe25-Ser26-Arg27-Ile28-Arg29-Arg30 in mouse, and Tyr24-Phe25-Ser26-Ser27-Ile28-Arg29-Arg30 in rat. (M1) comprises administering an antiproliferative agent. The transgene is operably linked to tissue-specific expression control sequences. Preferred Composition: (I) or (II) comprises uPA, where the uPA is incapable of binding to the uPA-receptor, and a carrier.

ABEX UPTX: 20031203

ADMINISTRATION - (I) or (II) is administered by parenteral, intravenous, intraarterial, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, or oral routes. No dosage given.

L84 ANSWER 3 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-679959 [64] WPIX

DNC C2003-185832

TI Predicting pathological conditions in heart failure using marker genes and proteins.

DC B04 D16

IN ASAKURA, M; FURUKAWA, H; ISOMURA, T; KITAKAZE, M; KOISHI, R; NAKAMARU, K; TAKASHIMA, S

PA (SANY) SANKYO CO LTD

CYC 30

PI WO 2003072824 A1 20030904 (200364)* JA 137p C12Q001-68

RW: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT SE
SI SK TR

W: AU CA IL US

JP 2004000155 A 20040108 (200405) 75p C12N015-09

ADT WO 2003072824 A1 WO 2003-JP2228 20030227; JP 2004000155 A JP 2003-50597
20030227

PRAI JP 2002-112228 20020415; JP 2002-54388 20020228

IC ICM C12N015-09; C12Q001-68

ICS A61K031-7088; A61K038-00; A61K039-395; A61K048-00; A61P009-04;
C12N015-12; C12Q001-02

AB WO2003072824 A UPAB: 20031006

NOVELTY - Predicting pathological conditions in heart failure using expression of one of 17:

(1) gene sequences encoding e.g. xenotropic retrovirus **receptor**, somatostatin **receptor** (isoform 1), G-protein coupled **receptor** (GPCR) 3, 15 or 35, endothelin type b **receptor**-like protein 2 galanin **receptor**, or formyl **receptor**, fully defined in the specification; or

(2) protein sequences encoded by the genes, fully defined in the specification, is new.

DETAILED DESCRIPTION - Predicting pathological conditions in heart failure using expression of one of 17:

(1) gene sequences encoding xenotropic retrovirus **receptor**, somatostatin **receptor** (isoform 1), G-protein coupled **receptor** (GPCR) 3, 15 or 35, endothelin type b **receptor**-like protein 2 galanin **receptor**, formyl **receptor**, coagulation factor II **receptor**-like 2 **proteinase-activated receptor** 3 or endothelial differentiation, sphingolipid GPC, fully defined in the specification; or

(2) protein sequences encoded by the genes, fully defined in the specification, is new.

INDEPENDENT CLAIMS are included for the following:

(1) medical compositions for treating heart failure containing the genes or proteins, antisense nucleic acids to the genes, or antibodies against the proteins; and

(2) a kit for carrying out the method.

ACTIVITY - Cardiant.

MECHANISM OF ACTION - Antisense therapy; Gene therapy; G-protein coupled **receptor** antagonist; Xenotropic retrovirus **receptor** antagonist; Somatostatin **receptor** antagonist; Formyl **receptor** antagonist. No biological data given.

USE - The proteins and genes are useful for diagnosis, treatment and prevention of heart failure.

Dwg.0/1

FS CPI

FA AB; DCN

MC CPI: B04-E03D; B04-E03F; B04-E06; B04-E12; B04-G01; B04-G04; B04-K01; B04-N02; B11-C08F; B12-K04A2; B14-F01B; B14-S03; **D05-H09**; D05-H11; D05-H12A; D05-H12D2

ABEX UPTX: 20031006

EXAMPLE - Using expression data from healthy heart tissue and that from a failed heart, G-protein coupled **receptor** (GPCR) gene data was extracted and marker genes that are expressed at different levels in healthy and diseases tissue were selected. The genes that showed an average difference value of more than 50 were those with nucleic acids sequences fully defined in the specification.

L84 ANSWER 4 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2002-750452 [81] WPIX

DNN N2002-591051 DNC C2002-212633

TI New isolated and purified **PAR-4** nucleic acid molecule and protein, useful for screening assays to detect compounds that bind to the protein or protein fragment, and for a small animal model of **thrombosis**.

DC B04 D16 S03

IN ADDO, M; ANDRADE-GORDON, P; DARROW, A; DERIAN, C

PA (ORTH) ORTHO-MCNEIL PHARM INC

CYC 100

PI WO 2002070564 A2 20020912 (200281)* EN 63p C07K014-705

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW

EP 1363947 A2 20031126 (200380) EN C07K014-705

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR

ADT WO 2002070564 A2 WO 2002-US5946 20020226; EP 1363947 A2 EP 2002-713702 20020226, WO 2002-US5946 20020226

FDT EP 1363947 A2 Based on WO 2002070564

PRAI US 2001-798279 20010302

IC ICM C07K014-705

ICS C07K016-28; C12N005-10; C12N015-12; G01N033-50

AB WO 200270564 A UPAB: 20021216

NOVELTY - An isolated and purified nucleic acid molecule (I) encoding guinea pig **Protease Activated Receptor-4** (**PAR-4**) protein comprises:

(i) sequence having at least 75% identity to a polypeptide with a fully defined sequence of 388 amino acids (S1), given in the specification;

(ii) complement of (i);

(iii) at least 15 sequential bases of (i) or (ii); and

(iv) sequence hybridizing under stringent conditions to (i).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) isolated and purified nucleic acid molecule (II) encoding a **PAR-4** fusion protein comprising at least amino acids 219-243 of guinea pig **PAR-4**;

(2) expression vector (III) for expression of a guinea pig **PAR-4** protein in a recombinant host, where the vector comprises a nucleic acid molecule that hybridizes under stringent conditions to a fully defined sequence of 1228 bp, given in the specification;

(3) substantially pure protein (IV) comprising a sequence of at least 15 consecutive amino acids corresponding to amino acids 219-243 of S1;

(4) recombinant host cell (V) comprising (III);

(5) monospecific antibody (VI) immunologically reactive with guinea pig **PAR-4** protein;

(6) cellular membrane fraction (VII) obtained from (V);

(7) expressing (M1) guinea pig **PAR-4** protein in a recombinant host cell comprising introducing (III) into suitable host cells, and culturing the host cells under conditions which allow expression of the guinea pig **PAR-4** protein;

(8) **PAR activating** peptide (VIII);

(9) monospecific antibody immunologically reactive with (VII);

(10) method (M2) comprising admixing in an aqueous environment a guinea pig **PAR-4 activating** peptide (AP) with a cell or tissue, incubating the **PAR-4 activating** peptide and the cell or tissue for a predetermined amount of time, and measuring the interaction of the peptide with the cells;

(11) promoting (M3) human **platelet aggregation** comprising combining an **aggregating** amount of an **activating** peptide with human **platelets** where the peptide comprises Sequence A;

(12) determining (M4) whether a substance is capable of inhibiting guinea pig **PAR-4** activity comprising giving a test substance and an **activating** peptide to a guinea pig, where the peptide comprises Sequence A, and measuring the ability of the test substance to inhibit **PAR-4 activation** in the guinea pig as compared to a control guinea pig that did not receive the substance;

(13) determining (M5) whether a substance capable of interfering with the interaction between an **activating** peptide and a **PAR-4** protein comprising adding a test substance and an **activating** peptide to a cell membrane composition comprising a **PAR-4** protein where the peptide comprises Sequence A, measuring the amount of binding of the peptide to the cell membrane composition, and comparing the amount of binding of the peptide to the composition to an amount of binding of the peptide in control cells receiving no test substance;

(14) compound identified by using M4 and M5; and

(15) peptide consisting of at least 15 consecutive amino acids from S1.

USE - (I) or the protein or protein fragment encoded is useful in screening assays to detect compounds that bind to the protein or protein fragment (claimed). The guinea pig **PAR-4** protein is useful in a small animal model of **thrombosis**. **PAR activating** peptides are useful as ligands to **activate** human **PAR4**.

Dwg.0/4

FS CPI EPI

FA AB; DCN

MC CPI: B04-B04D5; B04-C01C; B04-C01G; B04-E01; B04-F01; B04-F0100E; B04-G04; B04-G21; B04-K0100E; B04-N02A0E; B04-P01A; B11-C08; B11-C10; B12-K04A; B12-K04E; B14-L01; B14-L06; D05-C12; D05-H09; D05-H11A; D05-H12A; D05-H12D1; D05-H12E; D05-H14B2; D05-H17A4; D05-H18

EPI: S03-E14H4

TECH UPTX: 20021216

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Nucleic Acid: (I) is RNA or

DNA. (I) further comprises any of the fully defined sequences of 2428 or 1228 bp, given in the specification.

Preferred Vector: The expression vector comprises nucleic acid corresponding to any of the fully defined sequences of 2428 or 1228 bp, given in the specification. The expression vector encodes the guinea pig **PAR-4** protein of S1. The vector further comprises a genomic DNA encoding guinea pig **PAR-4** protein.

Preferred Protein: (IV) has a molecular weight of 41-55 kD. The protein further comprises S1.

(VIII) comprises the sequence (SEQUENCE A) SFPGQ(X)n where X = any amino acid or amino acid derivative and where

n = 0-30

Preferred Antibody: The antibody blocks activity of the guinea pig **PAR-4** protein, and is preferably a monoclonal antibody.

Preferred Method: The cell in M2 is in vitro or in vivo. The interaction of the peptide with the cell is detected by measuring the **activation** of a **PAR**. The cell membrane composition in M5 is a cell membrane fraction. The cell membrane composition is **part** of an intact cell or isolated tissue or organ sample. The cells are **platelets** and the measuring of the amount of binding comprises measuring the amount of **platelet aggregation**, calcium mobilization, ADP degranulation or cell shape change. M5 is preferably performed in a guinea pig. The **activating** peptide is labeled and the measuring of the amount of binding step comprises measuring the amount of label bound to the cell membrane composition.

Preparation: (I) was isolated using standard recombinant techniques.

ABEX UPTX: 20021216

SPECIFIC SEQUENCES - (I) has any of the specifically claimed fully defined sequences of 2428 or 1228 bp, given in the specification.

EXAMPLE - A probe corresponding to nucleotides 329-786 of human **PAR-4** was labeled by random priming and used to screen 3 x 10⁶ phage plaques of a gamma FIX II guinea pig genomic library under low stringency hybridization using Rapid-hyb Buffer for a minimum of 15 hours at 55degreesC. Washes were carried put with two 20 minutes washes of 2 x standard citrate saline/ 0.1% SDS and two 20 minute washes of 0.2 x SSC/ 0.1 % SDS at 55degreesC. 2 positives were isolated and following plaque purification, the entire genomic DNA inserts of both clones were independently subcloned into Not I site of the plasmid vector pKS II. A cross-hybridizing 1.3Kb Pst 1 restriction fragment, common to both genomic clones, was subcloned and subjected to sequence analysis. This fragment was found to contain all the coding sequence in exon2 from the presumptive **activation** sequence to the stop codon. sequence surrounding this Pst 1 fragment was obtained from the original guinea pig **PAR-4** genomic clones to partial sequence analysis and a compilation of this region is represented as a fully defined 2428 base pair sequence.

L84 ANSWER 5 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2002-698632 [75] WPIX

DNN N2002-550903 DNC C2002-197842

TI Preventing **platelet aggregation** or treating cardiovascular disorders related to **thrombotic** events comprises administering a histone compound .

DC B04 D16 P32

IN CLASS, R; **SOSLAU, G**; **ZEPPEZAUER, M**

PA (PHIL-N) PHILADELPHIA HEALTH & EDUCATION CORP; (SYMB-N) SYMBIOTEC GMBH

CYC 101

PI WO 2002067907 A1 20020906 (200275)* EN 13p A61K009-70

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR

KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT
 RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM
 ZW

EP 1370248 A1 20031217 (200402) EN A61K009-70

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR

ADT WO 2002067907 A1 WO 2002-US5157 20020222; EP 1370248 A1 EP 2002-706353
 20020222, WO 2002-US5157 20020222

FDT EP 1370248 A1 Based on WO 2002067907

PRAI US 2001-270759P 20010222

IC ICM A61K009-70

ICS A61F002-00; A61K009-22; A61K009-50; A61K031-00; A61K051-08;
 B01J013-08; C12N011-02

AB WO 200267907 A UPAB: 20021120

NOVELTY - Preventing **platelet aggregation** or treating
 cardiovascular disorders related to **thrombotic** events comprises
 administering a histone compound and a vehicle to the patient.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the
 following:

(1) composition for preventing **platelet aggregation**
 comprising a histone compound and a vehicle; or

(2) implantable device comprising a device that is coated with a
 histone compound that is to be inserted into the body of a patient.

ACTIVITY - Cardiant; Anticoagulant.

Test details are described but no results given.

MECHANISM OF ACTION - **Thrombin** inhibition by blocking
gamma -thrombin-induced platelet
aggregation.

USE - The method is useful for preventing **platelet**
aggregation or treating cardiovascular disorders related to
thrombotic events (claimed). Histone compounds can also be used to
 coat implantable devices such as stents or valves, or to coat devices
 inserted into the body of a patient, such as catheters.

Dwg.0/0

FS CPI GMPI

FA AB; DCN

MC CPI: B04-C01; B04-H0100E; B04-N0200E; B11-C04A; B14-F01; B14-F04; B14-L06;
 D05-C12; D05-H17A6

TECH UPTX: 20021120

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Compound: The histone
 compound, which is human, comprises H1, H2A, H2B, H3 or H4. H1 histone is
 a histone subtype H1.0, H1.1, H1.2, H1.3, H1.4 or H1.5 and is
 recombinantly produced. It is administered prophylactically.

ABEX UPTX: 20021120

SPECIFIC COMPOUNDS - The histone compound, which is human, comprises H1,
 H2A, H2B, H3 or H4. H1 histone is a histone subtype H1.0, H1.1, H1.2,
 H1.3, H1.4 or H1.5 and is recombinantly produced. H1 histone is a histone
 subtype H1.0, H1.1, H1.2, H1.3, H1.4 or H1.5.

ADMINISTRATION - Compositions in solution can be injected intravenously,
 intramuscularly, subcutaneously, intraperitoneally or instilled directly
 into the eye or mucosal areas. No dosage given.

L84 ANSWER 6 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2002-682036 [73] WPIX

DNC C2002-192387

TI Screening for **antithrombin** and **antiplatelet** compounds
 for treating cardiovascular disease comprises testing for inhibition of
GP Ib, PAR-1 or PAR-
4 receptor binding.

DC B04 D16

IN SOSLAU, G

PA (SOSL-I) SOSLAU G

CYC 1
PI US 2002103107 A1 20020801 (200273)* 5p C12Q001-56 <--
ADT US 2002103107 A1 Provisional US 2000-257067P 20001221, US 2001-29611
20011221
PRAI US 2000-257067P 20001221; US 2001-29611 20011221
IC ICM C12Q001-56
ICS A61K031-00
AB US2002103107 A UPAB: 20021113
NOVELTY - Screening (M1) for compounds with **antithrombotic/antiplatelet** activity comprising incubating test compounds with **platelets** in vitro and testing for ability to inhibit **platelet aggregation** through inhibition of:
(a) **GP Ib, PAR-1** or **PAR-4 receptor** binding; or
(b) **alpha -thrombin, beta -thrombin** or **gamma-thrombin pathways**,
is new.
USE - (M1) is useful for screening for compounds with **antithrombotic/antiplatelet** activity (claimed) which may be useful in treating cardiovascular disease.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-F04; B04-H19; B04-K01R; B04-N06; B11-C07B; B11-C08E1; B12-K04E; B14-F01; D05-H09
ABEX UPTX: 20021113
EXAMPLE - No suitable example is given.

L84 ANSWER 7 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-315494 [35] WPIX
DNN N2002-246915 DNC C2002-091848
TI Identifying agent inhibiting **thrombin-induced platelet activation**, by administering test agent and proteolytically inactive **thrombin** to **GP V** null non-human transgenic animal and monitoring **platelet aggregation**.
DC B04 D16 P14 S03
IN PHILLIPS, D; RAMAKRISHNAN, V
PA (CORT-N) COR THERAPEUTICS INC
CYC 97
PI WO 2002017711 A2 20020307 (200235)* EN 64p A01K067-027
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO
RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001086900 A 20020313 (200249) A01K067-027
ADT WO 2002017711 A2 WO 2001-US26936 20010831; AU 2001086900 A AU 2001-86900
20010831
FDT AU 2001086900 A Based on WO 2002017711
PRAI US 2000-230566P 20000831; US 2000-229047P 20000831
IC ICM A01K067-027
ICS A61P007-00; G01N033-86
AB WO 200217711 A UPAB: 20020603
NOVELTY - Identifying (M1) agent that inhibits **thrombin (T)-induced activity (A)** (e.g., **platelet (P) activation**), where (A) is modulated (inhibited) by **GP V**, by administering test agent and (proteolytically inactive) (T) to a **GP V** null non-human transgenic animal (I), and monitoring **aggregation of (P)** of (I) to identify inhibition. (M1) optionally involves using (P) isolated from (I) to identify modulator of (T), is new.
DETAILED DESCRIPTION - Identifying (M1) agent that inhibits **thrombin (T)-induced activity (A)** (e.g., **platelet (P)**)

activation), where (A) is modulated (inhibited) by GP V, by administering test agent and (proteolytically inactive) (T) to a GP V null non-human transgenic animal (I), and monitoring **aggregation** of (P) of (I) to identify inhibition. (M1) optionally involves using (P) isolated from (I) to identify modulator of (T). (M1) involves administering test agent and (proteolytically inactive) (T) to (I), and monitoring **aggregation** of (P) of (I) to identify inhibition. Optionally (M1) involves administering a test agent and (T) using (P) isolated from (I) and monitoring **aggregation** of (P) for modulation of the activity. Screening for anti-**thrombotic** agents alternatively involves contacting (P) that does not display GP V on its surface within agent, contacting (P) with the GP Ib-IX signaling **activator**, and determining GP Ib-IX mediated signal transduction level, where a reduced level is indicative of an anti-**thrombotic** agent. Identifying (M1) an agent that inhibits **thrombin**-induced **platelet activation**, where the **activation** is modulated by GP V, involves administering a test agent and proteolytically inactive **thrombin** to a (I), and monitoring **aggregation** of **platelets** of the animal to identify inhibition. Identifying (M2) an agent that inhibits **thrombin**-induced activity, where the activity is inhibited by GP V involves administering a test agent and **thrombin** to a **platelet** isolated from (I) and monitoring **aggregation** of **platelets** to identify modulation of activity. Identifying an agent that modulates **thrombin** activity, where the activity is inhibited by GP V involves administering a test agent and **thrombin** to **platelet** isolated from (I) and monitoring **aggregation** of **platelets** to identify modulation of activity.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition (II) comprising a **platelet** that does not display GP V on its surface; and a GP Ib-IX signaling **activator**;

(2) determining (M2) predisposition to **thrombosis** in a subject by determining level of GP V α 1 in a blood sample from the subject, where GP V α 1 presence in the sample indicates predisposition to **thrombosis**. The method optionally involves determining level of GP V on **platelets** derived from the subject, where decrease in the level of GP V on **platelets** is indicative of the predisposition **thrombosis**;

(3) inhibiting (M3) **thrombosis** in a subject involves administering to a subject, an inhibitor of GP Ib-IX signal transduction, with the proviso that the agent is not heparin;

(4) screening (M4) for **antithrombotic** agents, involves contacting a **platelet** that does not display GP V on its surface with an agent, contacting the **platelet** with a GP Ib-IX signaling **activator**, and determining GP Ib-IX mediated signal transduction level, where a reduced level is indicative of an **antithrombotic** agent;

(5) preventing (M5) **platelet activation** in a subject, involves administering to the subject an agent that prevents interaction of **thrombin** exosite II with GP Ib-IX, with the proviso that the agent is not heparin;

(6) an agent (III) identified by (M1), where proteolytically inactive (T) is administered to (I); and

(7) a pharmaceutical composition (IV) comprising (III) to ameliorate a condition characterized by **platelet activation**.

ACTIVITY - Anticoagulant. No supporting data is given.

MECHANISM OF ACTION - **Platelet activation** inhibitor; GP Ib-IX signal transduction inhibitor; interaction of (T) exosite II with GP Ib-IX inhibitor.

USE - For identifying agents that inhibit (T)-induced activity e.g., (T)-induced (P) **activation**, and for screening anti-thrombotic agents. (M3) is useful for inhibiting **thrombosis** in a subject. (M5) is useful for preventing (P) **activation** in a subject (all claimed).

Dwg.0/14

FS CPI EPI GMPI

FA AB; DCN

MC CPI: B04-B04D5; B04-F04; **B04-H19**; B04-P0100E; B11-C08D;

B12-K04E; B14-F04; D05-H08; **D05-H09**; D05-H11

EPI: S03-E14H1

TECH UPTX: 20020603

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: (T) used in (M1) may be proteolytically inactive, or may be an active (T). The proteolytically inactive (T) is phenylalaninylprolylargininylchlormethylketone (PPACK)-inactivated (T), S205A (T), or di-isopropylphospho (DIP)-(T). The test agent administered to (I) along with proteolytically inactive (T) binds **Ib-IX**, and is an antibody that specifically binds to **GP Ib-IX** or is an agent that binds exosite II of (T).

The test agent administered along with active (T), is an antibody that binds specifically to **GP Ib-IX**, peptide or small molecule. The **GP Ib-IX activator** is inactive

(T), e.g., proteolytically inactive (T). The **GP Ib-IX-mediated** signal transduction level is determined by measuring (P)

aggregation. In (M2), determining level of **GP V_{f1}** is

performed using an antibody specific for **GP V_{f1}**. Determining

level of **GP V** on (P), is performed by fluorescence

activated cell sorting (FACS) or by Western blot. In (M3), the

inhibitor binds to exosite II of (T).

Preferred Composition: (II) contains a **GP Ib-IX**

signaling **activator** which is a proteolytically inactive (T).

(II) further comprises an agent that modulates an activity of (P) induced by (T). The (T) used in the method may be a proteolytically inactive (T) as described above.

ABEX UPTX: 20020603

WIDER DISCLOSURE - The following are also disclosed as new:

(1) non-human transgenic animal (V), preferably mammals that contain or comprise a modified **GP V** gene;

(2) cells isolated from (V);

(3) preparing (V);

(4) comparing a characteristic between two mammals of same species, or strain, where one mammal has, for e.g., a wild-type **GP V** gene and the other mammal has a modified **GP V** gene; and

(5) comparing cells isolated from (V).

ADMINISTRATION - The agents are administered by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal or buccal route. Dosages range from 0.1-100 (preferably 0.1-1) microg/kg body weight.

EXAMPLE - To evaluate the specific role of **glycoprotein V** (

GP V) in both **platelet** function and the **GP**

Ib-IX-V complex expression, a mouse strain that lacked the

GP V gene was generated using homologous recombination techniques.

Analysis of whole blood from **GP V**-deficient animals showed the

platelets were normal in both number and size. **Platelet**

counts in whole blood were within the normal range. There was a

statistically significant difference in **platelet** recovery from whole blood from wild-type animals and -/- animals. +/- animals showed intermediate recovery numbers, which were not statistically different.

Platelets were isolated from the -/- animals to confirm that gene

deletion resulted in absence of **GP V** protein expression and

analyzed for **GP V** expression using **GP V** antibodies. No

GP V protein was detectable either on the intact **platelet**

surface using fluorescence **activated** cell sorting (FACS)

analysis or in total **platelet** lysates as determined by Western blotting. 2 assays were used to determine whether the **GP Ib** expressed on **GP V -/- platelets** was functional. One assay measured the adhesion of **platelets** to immobilized von Willebrand factor (vWf) that was **activated** by botrocetin to bind **GP Ib**. The **GP V -/- platelets** bound to immobilized, botrocetin-activated human vWf in a manner indistinguishable from wt **platelets**. Under these conditions, the binding of vWf to **platelets** was mediated entirely by **GP Ib**, since purified human glyocalicin (a soluble, extracellular fragment of **GP Ibalpha** that contains the vWf binding domain), inhibited botrocetin-induced binding of **platelets** to vWf in a concentration-dependent manner. Also the soluble, **activated** vWf bound identically to **platelets** from all 3 genotypes. Again, botrocetin-induced vWf binding could be completely inhibited by purified glyocalicin. Furthermore, stimulation of **alphaIIb beta3** on **platelets** by ADP and epinephrine did not induce soluble vWf binding. Thus, **GP Ib-IX** expressed in the **GP V -/- platelets** was functional. The effect of **GPV** gene deletion on **thrombin**-induced **platelet** function was determined and results showed that **GP V** was a negative regulator of **platelet** function. Since **platelets** lacking **GP V** exhibited an increased **aggregation** response to **thrombin** compared to wt **platelets**. To determine the consequences of enhanced **platelet** function in **GP V -/-** mice, bleeding time measurements were performed using a tail cut model. **GP V -/-** mice had a statistically shorter bleeding time than wt littermate control mice. 70% of the **-/-** mice had bleeding times less than 120 sec, compared to 50% of the wt and **+/-** mice. Conversely, 21.6% of the wt mice had bleeding times greater than 500 sec, compared to 9.5% in the **+/-** mice and 8.5% in the **-/-** mice. Thus the increased aggregability of the **platelets** from **GP V -/-** mice observed in in vitro assays translates into a shorter bleeding time in vivo. To evaluate the physiological significance of the ligand binding function of **thrombin**, the effect of a systemic infusion of **DIP-thrombin** into mice was examined. Infusion of a **platelet** agonist induces a decrease in **platelet** counts due to (ongoing) **thrombosis**. There was significant **platelet** loss following the infusion of 10 nM **thrombin** in both **GP V** null and wt mice. Injection of 1 nM **thrombin** had a marginal effect on **platelet** counts in either **GP V** null mice or wt mice. In contrast, **GP V** null mice showed a significant **platelet** loss was minimal. As additional controls mutant CHO-expressed **thrombins** was used in which the exosite II has been mutated (R89/R93/E94 and R98A). These exosite II mutants were inactivated, and then injected into either **GP V** null or wt mice. There was no major loss in **platelets**. In contrast, 460 nM CHO-expressed inactivated **thrombins** caused a significant **platelet** loss in **GP V** null mice, with little effect in wt mice. These results showed that binding of inactive forms of **thrombin** to **GP V**-deficient **platelets** can occur in vivo, and that the binding results in **platelet** **activation** and **thrombosis**. The data further substantiate the binding site for **GP Ibalpha** being via exosite II of **thrombin**. These results support a novel role for **GP Ibalpha** in **thrombin**-induced signaling in **platelets** which consequently supports **aggregation** and **thrombosis**. From further experiments carried out, a model for **thrombin**-induced **platelet** **activation** was established that involved not only the established **pathway** mediated by the **protease activated receptors (PARs)**, but also a novel **pathway** in which the presence of **GP V**

in the GP Ib-IX-V complex inhibits the ability of **thrombin** to function as a **receptor** ligand. Following the loss of GP V upon cleavage by **thrombin**, **thrombin** binding to GP Ibalpha results in **activation** of alphaIIb beta3 and consequently in **aggregation**. Thus, the GP Ibalpha-bound **thrombin** need not be catalytically functional for this response to occur. The data show not only a novel functional role for **thrombin**, but also a novel mechanism by which this **pathway** can mediate **thrombosis** independent of proteolytic activity.

L84 ANSWER 8 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2002-188255 [24] WPIX

DNN N2002-142767 DNC C2002-058072

TI New peptides modulating **protease-activated receptors**, useful for modulating **platelet activation** including clotting, particularly for treating e.g. myocardial infarction, stroke, pulmonary embolism or hemorrhage.

DC B04 D16 S03

IN COUGHLIN, S R; FARUQI, T R

PA (REGC) UNIV CALIFORNIA

CYC 21

PI WO 2001094411 A1 20011213 (200224)* EN 98p C07K014-705
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA JP US

ADT WO 2001094411 A1 WO 2000-US28958 20001019

PRAI US 2000-587718 20000605

IC ICM C07K014-705

ICS A61K038-08; A61P007-02; C07K007-06; G01N033-68

AB WO 200194411 A UPAB: 20020416

NOVELTY - Isolated peptides comprising peptides that **activate protease-activated receptors (PAR)** 1 or **PAR4**, are new.

DETAILED DESCRIPTION - The **PAR1** modulating peptide comprises GYPAKF, GYP(Cha)KF, GYPLKF, GYPIKF, S(F)(Cha)(Cha)(homoR)K or S(F)(Cha)(Cha)RK. The **PAR4** modulating peptide comprises GYPGRF, GYPG(homoR)F, GYPG(Orn)F, GYPGKY, GYPGKW, GYPGKK, SYPAKF, SYAGKF, SYPGRF or SYPG(homoR)F.

(Cha) = cyclohexylalanine;

(F) = parafluoro-phenylalanine;

(homoR) = homoarginine; and

(Orn) = ornithine.

INDEPENDENT CLAIMS are also included for the following:

(1) an expression vector comprising a polynucleotide encoding any of the isolated peptides;

(2) a host cell comprising the expression vector;

(3) pharmaceutical agents comprising: (a) the isolated peptides and a pharmaceutical excipient; (b) an isolated peptide selected from AYPGKF, SYPGKF or TYPGKF, and a pharmaceutical excipient; or (c) an isolated peptide selected from GFPGKF or G(F)PGKF, and a pharmaceutical excipient;

(4) methods for modulating **PAR4** activity or **PAR1** activity in an individual by administering the pharmaceutical agent to the individual;

(5) methods for modulating **platelet activation** in an individual by administering the agent to the individual;

(6) methods for modulating both **PAR1** and **PAR4** activity in an individual by administering the agent of (3c) to the individual;

(7) methods for identifying an agent that modulates **PAR4** or **PAR1** activity comprising: (a) contacting a host cell comprising **PAR4** or **PAR1** function with the agent to be tested, and the **PAR4** or **PAR1** activating peptide; and (b) analyzing at least one characteristic that is associated with **PAR4**.

or **PAR1** function in the host cell, where an agent is identified by its ability to modulate at least one such characteristic as compared to contacting the host cell with the **PAR4** or **PAR1** activating peptide without the agent;

(8) a method for identifying an agent that modulates both **PAR1** and **PAR4** activity comprising: (a) contacting a host cell comprising **PAR1** function with the agent to be tested and the **PAR1** and analyzing at least one characteristic that is associated with **PAR1** function in the host cell, where an agent is identified by its ability to modulate at least one such characteristic as compared to contacting the suitable host cell with the **PAR1** activating peptide without the agent; (b) contacting a host cell comprising **PAR4** function with the agent to be tested and the **PAR4** activating peptide and analyzing at least one characteristic that is associated with **PAR4** function in the host cell, where an agent is identified by its ability to modulate at least one such characteristic as compared to contacting the suitable host cell with the **PAR4** activating peptide without the agent; and (c) selecting an agent that modulates at least one characteristic associated with **PAR1** function and at least one characteristic associated with **PAR4** function, where the steps (a) and (b) are performed in any order or simultaneously;

(9) kits comprising any of the isolated peptides cited above; and

(10) a method for identifying an agent that antagonizes **PAR1** or **PAR 4** activity comprising: (a) contacting a host cell comprising **PAR1** or **PAR4** function with the agent to be tested and the **PAR1**; and (b) analyzing at least one characteristic that is associated with **PAR1** or **PAR4** function in the host cell, where an agent is identified by its ability to modulate at least one such characteristic as compared to contacting the suitable host cell with the **PAR1** or **PAR4** activating peptide without the agent.

ACTIVITY - Cerebroprotective; cardiant; antiarteriosclerotic; hemostatic; vulnerary.

No supporting data provided.

MECHANISM OF ACTION - **PAR** (protease-activated receptors) modulator.

The relative potencies of the peptides GYPGKF (native), SYPGKF and AYPGKF in phosphoinositide hydrolysis and cytoplasmic assays in KOLF-**PAR4** cells were compared. GYPGKF appeared to be a partial agonist for **PAR-4** triggered phosphoinositide hydrolysis; even at 500 micro m it elicited only approximately 50% of the maximal response to **thrombin**. SYPGKF and AYPGKF were full agonists for **PAR4** activation and showed EC50's of 20 and 50 micro M respectively. AYPGKF stimulated calcium mobilization in KOLF-**PAR4** cells with an EC50 of 25 micro M, while more than 200 micro M of GYPGKF was required to elicit a similar response, showing that AYPGKF was more potent than GYPGKF. These data suggest that AYPGKF is intrinsically more active than GYPGKF at **PAR-4**.

USE - The peptides are useful for modulating **PAR1** or **PAR4**. In particular, the peptides are useful as therapeutic and/or prophylactic vaccines for modulating **platelet activation** including clotting. The peptides are useful for inhibiting inappropriate clotting in an individual, particularly for treating disorders such as myocardial infarction, stroke, pulmonary embolism, deep vein **thrombosis**, peripheral arterial occlusion or other blood system **thromboses**. The peptides are also useful for **activating** blood clotting in an individual to treat disorders involving insufficient clotting, e.g. hemorrhage. The peptides may also be used as an agent to screen pharmaceutical candidates (both in vitro and in vivo) or in drug design. In the method of (8), the host cell of step (a) lacks native **PAR1** function and comprises a recombinant polynucleotide encoding **PAR1** or its functional fragment, where **PAR1** function is

restored in the host cell. The host cell of step (b) has native **PAR4** function, where the host cell of step (b) lacks native **PAR4** function and comprises a recombinant polynucleotide encoding **PAR4** or its functional fragment, and where **PAR4** function is restored in the host cell. The method also involves identifying antagonists or agents that antagonize **PAR4** or **PAR1** activity by analyzing at least one characteristic associated with the inhibition of **PAR4** or **PAR1** activation in the host cell. An agent is identified by its ability to modify at least one such characteristic as compared to contacting the host cell with the **PAR4** or **PAR1** activating peptide without the agent.

DESCRIPTION OF DRAWING(S) - Figure showing calcium mobilization in human platelets following **PAR4** desensitization. Washed human platelets were loaded with FURA-2/AM and agonist triggered increases in cytosolic calcium was measured fluorometrically.

Dwg.0/8

FS CPI EPI

FA AB; DCN

MC CPI: B04-C01B; B04-E08; B04-F0100E; B11-C08E; B12-K04E;
B14-D07C; B14-F01B; B14-F04; B14-F08; B14-K01; B14-N16;
D05-H09; D05-H12D6; D05-H12E; D05-H14

EPI: S03-E14H

TECH UPTX: 20020416

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preparation: The peptides can be produced by recombinant methods or by chemical synthesis. Preferred Peptide: The peptide may be AYPGKF. The host cell has native **PAR4** or **PAR1** function. The host cell may also lack native **PAR4** or **PAR1** function, and comprises a recombinant polynucleotide encoding **PAR4** or **PAR1** or their functional fragment, where **PAR4** or **PAR1** function is restored in the host cell. In particular, the host cell is a platelet cell. The characteristic that is associated with **PAR4** or **PAR1** function is phosphoinositide hydrolysis, intracellular calcium mobilization, platelet shape change, platelet ATP (adenosine triphosphate) secretion or platelet aggregation.

ABEX UPTX: 20020416

ADMINISTRATION - Administration is by injection (e.g. intraperitoneally, intravenously, subcutaneously or intramuscularly). The amount of the agent is 0.001-100 mg/kg, preferably 0.01-10 mg/kg body weight of the individual (claimed) per week.

EXAMPLE - No relevant example given.

L84 ANSWER 9 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2001-656678 [75] WPIX

DNC C2001-193094

TI Peptides comprising an amino acid sequence are capable of stimulating protease-activated receptor 4 which are useful in diagnosis and therapy e.g. inhibiting tumor cell proliferation and stimulating platelet aggregation.

DC B04 D16

IN BAINBUR, N; WEST, R R

PA (ZYMO) ZYMOGENETICS INC

CYC 94

PI WO 2001058930 A1 20010816 (200175)* EN 84p C07K007-06

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001033333 A 20010820 (200175) C07K007-06
 EP 1254160 A1 20021106 (200281) EN C07K007-06
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI TR

ADT WO 2001058930 A1 WO 2001-US3807 20010206; AU 2001033333 A AU 2001-33333
 20010206; EP 1254160 A1 EP 2001-905455 20010206, WO 2001-US3807 20010206

FDT AU 2001033333 A Based on WO 2001058930; EP 1254160 A1 Based on WO
 2001058930

PRAI US 2000-500646 20000209

IC ICM C07K007-06

ICS A61K038-08; C07K014-705

AB WO 200158930 A UPAB: 20011220

NOVELTY - A peptide (I) comprising an amino acid sequence is new.

DETAILED DESCRIPTION - A peptide (I) comprises an amino acid sequence
 selected from

(a) Gly-Tyr-Pro-Gly-Gln-Val-Cys-NH₂;

(b) Gly-Tyr-Pro-Gly-Gln-Val-Cys-Ala-NH₂; and

(c) Gly-Xaa1-Pro-Gly-Lys-Xaa2-Xaa3-NH₂,

Xaa1 = Tyr, Tyr(Me), Bip or 2-Nal;

Xaa2 = Phe, hPhe, Phe(4-F), Phe(4-Me), Thi, 1-Nal, 2-Nal or Bip; and

Xaa3 = Cys or Pen.

INDEPENDENT CLAIMS are also included for:

(1) a composition comprising a carrier and a peptide (I);

(2) a method of stimulating **platelet aggregation**

by administering the composition to **platelets**; and

(3) a method of inhibiting tumor cell proliferation by administering
 the composition to tumor cells.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - **Protease-activated
 receptor 4** stimulator.

USE - (I) are capable of stimulating **protease-
 activated receptor 4** which are useful in diagnosis and
 therapy e.g. inhibiting tumor cell proliferation and stimulating
platelet aggregation.

ADVANTAGE - (I) mimic the N-terminus of the **activated** form
 of **protease-activated receptor 4**.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B04-C01B; B14-F08; B14-H01B; B14-L01; D05-H09

ABEX UPTX: 20011220

SPECIFIC POLYPEPTIDES - The following peptides are specifically claimed:

Gly-Tyr-Pro-Gly-Lys-hPhe-Cys-NH₂, Gly-Tyr(Me)-Pro-Gly-Lys-Phe-Cys-NH₂,

Gly-Tyr-Pro-Gly-Lys-Phe(4-F)-Cys-NH₂,

Gly-Tyr-Pro-Gly-Lys-Phe(4-Me)-Cys-NH₂,

Gly-Bip-Pro-Gly-Lys-Phe-Cys-NH₂,

Gly-2Nal-Pro-Gly-Lys-Phe-Cys-NH₂,

Gly-Tyr-Pro-Gly-Lys-Phe-Pen-NH₂, and

Gly-2Nal-Pro-Gly-Lys-Phe-Pen-NH₂.

ADMINISTRATION - The composition is administered to a mammalian subject
 (claimed). Administration may be e.g. intravenous, intraarterial,
 intraperitoneal, intramuscular or oral. Dosage is 1 pg/kg to 10 mg/kg.

EXAMPLE - No preparative examples are given.

L84 ANSWER 10 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2001-226546 [23] WPIX

DNC C2001-067598

TI Inhibiting **thrombin activation** in human cell
 expressing **protease activated receptor 1** (
PAR1), comprises contacting mixtures of **thrombin** and
 human cell expressing **PAR1**, with a peptide that inhibits

platelet activation.

DC B04
 IN HASAN, A A K; SCHMAIER, A H
 PA (THRO-N) THROMGEN INC; (UNMI) UNIV MICHIGAN
 CYC 95
 PI WO 2001012656 A1 20010222 (200123)* EN 49p C07K007-06
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SD SE SL SZ TZ UG ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
 DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
 LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
 SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
 AU 2000078822 A 20010313 (200134) C07K007-06
 EP 1212352 A1 20020612 (200239) EN C07K007-06
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
 RO SE SI
 JP 2003507389 W 20030225 (200317) 58p C07K007-18
 US 6544750 B1 20030408 (200327) G01N033-53
 AU 764707 B 20030828 (200361) C07K007-06
 ADT WO 2001012656 A1 WO 2000-US40669 20000817; AU 2000078822 A AU 2000-78822
 20000817; EP 1212352 A1 EP 2000-968987 20000817; WO 2000-US40669 20000817;
 JP 2003507389 W WO 2000-US40669 20000817; JP 2001-517554 20000817; US
 6544750 B1 US 1999-375808 19990817; AU 764707 B AU 2000-78822 20000817
 FDT AU 2000078822 A Based on WO 2001012656; EP 1212352 A1 Based on WO
 2001012656; JP 2003507389 W Based on WO 2001012656; AU 764707 B Previous
 Publ. AU 2000078822, Based on WO 2001012656
 PRAI US 1999-375808 19990817
 IC ICM C07K007-06; C07K007-18; G01N033-53
 ICS A61K038-00; A61P007-02; C07K007-08
 AB WO 200112656 A UPAB: 20010425
NOVELTY - Inhibiting thrombin activation in a human
cell expressing protease activated receptor
1 (PAR1), comprises providing a mixture comprising
thrombin at a concentration effective to induce stimulus-response
coupling within the cell, and a human cell expressing PAR1, and
contacting the mixture with a compound (I) and (II) comprising at least
one segment with an amino acid sequence (S1).
DETAILED DESCRIPTION - S1 is of formula Arg-Gly-Lys-Z4-Cys (I) or
Arg-Gly-Asp-Z4-Cys (II), where Z4 is any naturally occurring amino acid,
excluding cysteine. (I) comprises at most 10 amino acids in sequence.
INDEPENDENT CLAIMS are also included for the following:
(1) a method of binding a compound to biotinylated-peptide
NATLDPRSFLLR (biotin-NAT12), providing a compound comprises (I) or (II),
and incubating biotinNAT12 with (I) or (II); and
(2) a compound (I) comprising S1.
ACTIVITY - Anticoagulant.
MECHANISM OF ACTION - Inhibitor of platelet
aggregation; inhibitor of thrombin activation;
inhibitor of thrombin induced calcium mobilization in
fibroblasts (claimed).
 Fresh whole blood was collected and mixed with 0.013 M sodium citrate
 and platelet-rich plasma was prepared. Platelet-rich
 plasma with a normalized platelet count between 2-2.5 multiply
 108 platelets/ml was added to a cuvette of an aggregometer.
 Peptides to be examined were added to the cuvette and the mixture
 stabilized for a few moments. Once the baseline was stabilized,
 gamma -thrombin was added to determine the minimal
 concentration of the agonist necessary to achieve full platelet
 aggregation. Aggregation was allowed to proceed for 5
 minutes before stopping. When ADP-induced platelet
 aggregation studies were performed, 1-5 mu M ADP was added to the
 cuvette containing platelet-rich plasma. 70 nM gamma -
 thrombin induced a full platelet aggregatory

response. The **aggregation** response was abolished by 0.5-1 mM RPPGF. At 0.25 mM RPPGF, **gamma -thrombin-induced platelet aggregation** was completely inhibited. RGKWC, **gamma -thrombin-induced platelet aggregation** returned to levels seen without any inhibitor. The most potent to least potent inhibitors of **gamma -thrombin-induced platelet aggregation** are RGKLC, RGKTC, RGKRC, RGKIC, RGKWC, RGKYC, and RGKMC in decreasing order.

USE - The invention is useful for preventing **thrombosis**, where **thrombosis** is defined as occlusion of a vessel due to formation of a **platelet-rich**, **fibrin-rich**, or a mixed **platelet-fibrin thrombus** (claimed). The invention can be used for patients with acute coronary syndromes (e.g. crescendo angina, myocardial infarction) and for individuals who have acute coronary syndromes and receive percutaneous transluminal coronary angioplasty with an artificial stent placement.

Dwg.0/6

FS CPI

FA AB; DCN

MC CPI: B04-C01A; B04-C01B; B04-C01C; **B04-H19**; B14-F01B; B14-F04

TECH UPTX: 20010425

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: The method further comprises inhibiting **thrombin** induced calcium mobilization in fibroblasts. The method preferably comprises inhibiting **thrombin activation** in a sample comprising blood **platelets**, which involves providing a solution comprising blood **platelets** and **thrombin** at a concentration effective to cause **platelet aggregation**, and contacting the blood sample with (I) or (II). The method further involves inhibiting **thrombin** induced **platelet aggregation**.

Preferred Composition: **Thrombin** comprises **alpha-thrombin** and/or **gamma-thrombin**.

(I) or (II) comprises at most 5 amino acids in sequence. The cell comprising **PAR1** is selected from **platelets**, endothelial cells, brain cells, fibroblasts or smooth muscle cells.

ABEX UPTX: 20010425

SPECIFIC SEQUENCES - S1 comprises a sequence selected from any one of the 17 sequences of 5 amino acids in length, of (I), such as Arg-Gly-Lys-Leu-Cys, or from any one of the 18 sequences of 5 amino acids in length, of (II), such as Arg-Gly-Asp-Trp-Cys (claimed).

ADMINISTRATION - The purified peptides of the invention may be used prophylactically in surgery or catheterization for insertion of artificial dacron grafts and stents to prevent reocclusion. Administration includes intravenous, intranasal, or oral or preferably parentally. Dosages range from 10 to 30 mg per day per kg of body weight. In preferred intravenous administration the dosage is 10 mg/kg body weight in 5 ml of normal saline or in a suitable vehicle at 1 ml/min.

EXAMPLE - Three successive combinatorial libraries were prepared to obtain the peptide analogs. The first library started with the peptide Arg-Pro-Pro-Gly-Phe. Investigations showed that an alanine substitution in the peptide at position 1 at N-terminal end resulted in marked loss of **thrombin** inhibitory activity. Alternatively, substitution in the fifth position at C-terminal end of a cysteine for a phenylalanine did not result in any loss of activity. Since cysteine in this fifth position promoted binding of the peptides to plastic plates, all subsequent peptides had cysteine placed at this position. The initial positional peptide combinatorial library consisted of H-RO2XXC-NH₂, H-RXO3XC-NH₂ and H-RXXO4C-NH₂, where O₂, O₃ or O₄ represents all L-amino acids from A to Y, except cysteine, and X is an equimolar mixture of L-amino acids from A to Y, except cysteine. Investigations revealed that a glycine in the second position produced a peptide(s) with best ability to inhibit **thrombin-induced platelet aggregation**, to

inhibit **thrombin**-induced calcium mobilization, and to bind biotin-NAT112 (peptide sequence Asn-Ala-Thr-Leu-Asp-Pro-Arg-Ser-Phe-Leu-Leu-Arg that spans the **alpha-thrombin** cleavage site on the **thrombin receptor**). A second peptide combinatorial library was designed to examine the third and fourth position of this sequence. Peptides H-RGO3XC-NH2 and H-RGX04C-NH2 were prepared where O3 and O4 were all L-amino acids from A to Y, except cysteine, and X was an equimolar mixture of L-amino acids from A to Y, except cysteine. Investigations revealed that a lysine or aspartic acid in the third position produced peptides with best ability to inhibit the above-mentioned processes. A third library was prepared where the third positions were fixed as a lysine or aspartic acid, H-RGK04C-NH2 and H-RGDO4C-NH2, where O4 is all L-amino acids except cysteine. A standard solid phase automated peptide synthesis was utilized to prepare the peptide libraries. Synthetic peptide libraries were prepared using methylbenzhydrylamine (MBHA) polystyrene resin and standard t-Boc chemistry in combination with simultaneous multiple peptide synthesis (SMPS). A peptide synthesis resin was prepared that assures equimolarity of the peptides on the resin. Nineteen porous polypropylene packets, each containing 4.65 mmol of MBHA resin, were coupled to each of the protected N-**alpha**-t-Boc amino acids of interest. Cysteine was excluded from coupling mixture. The resulting resins from each packet were combined and thoroughly mixed. The resin mixture was then separated into 19 portions of equal weight which were then placed into porous polypropylene packets, followed by N-**alpha**-t-Boc protecting group removal and neutralization of the resulting amine TFA salts. Resin packets were then reacted with solutions of the individual **activated** amino acids to yield the various peptide combinations. The peptide mixtures were deprotected and then cleaved from their respective resins using low-high hydrogen fluoride. Extraction of the individual peptide mixtures was carried out with water or dilute acetic acid and the solutions lyophilized.

L84 ANSWER 11 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
 AN 1999-633640 [54] WPIX
 DNC C1999-185014
 TI Novel **protease activated receptor 4**, useful
 for screening for (ant)agonists for promoting the proliferation and/or
 differentiation of **platelets** and in mediating inflammatory
 events.
 DC B04 D16
 IN FOSTER, D C; PRESNELL, S R; XU, W; YEE, D P
 PA (UNIW) UNIV WASHINGTON; (Zymo) ZYMOGENETICS INC; (FOST-I) FOSTER D C;
 (PRES-I) PRESNELL S R; (XUWW-I) XU W; (YEED-I) YEE D P
 CYC 82
 PI WO 9950415 A2 19991007 (199954)* EN 85p C12N015-12
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
 OA PT SD SE SL SZ UG ZW
 W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE
 GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG
 MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG
 UZ VN YU ZW
 AU 9934591 A 19991018 (200010)
 US 6111075 A 20000829 (200043) C07K007-06
 US 6436400 B1 20020820 (200257) C07K016-28
 US 2003143218 A1 20030731 (200354) A61K038-48
 ADT WO 9950415 A2 WO 1999-US7100 19990331; AU 9934591 A AU 1999-34591
 19990331; US 6111075 A US 1998-53866 19980401; US 6436400 B1 Div ex US
 1998-53866 19980401, US 2000-479130 20000107; US 2003143218 A1 Cont of US
 1998-53866 19980401, Div ex US 1999-371333 19990810, Div ex US 2000-479130
 20000107, Div ex US 2000-480720 20000107, US 2002-187049 20020628
 FDT AU 9934591 A Based on WO 9950415; US 6436400 B1 Div ex US 6111075; US
 2003143218 A1 Cont of US 6111075, Div ex US 6436400

PRAI US 1998-53866 19980401; US 2000-479130 20000107

IC ICM A61K038-48; C07K007-06; C07K016-28; C12N015-12

ICS A61K038-17; C07H021-04; C07K007-08; C07K014-705; C12N005-06;
C12P021-02

AB WO 9950415 A UPAB: 20010312

NOVELTY - A **protease activated receptor 4** (

PAR4) polypeptide (I), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated polynucleotide (PN) (II) encoding (I), comprising nucleotides 176 to 1330 of the 4895 base pair sequence fully defined in the specification (I), or its derivatives;

(2) an isolated **PAR4** ligand (III), comprising amino acids 48 (Gly) to 53 (Val) of (I), or allelic variants or orthologs of (III);

(3) an isolated polynucleotide encoding (III), comprising nucleotides 317 to 409 of the 4895 nucleotide sequence fully defined in the specification, or its derivatives;

(4) an expression vector (IV) comprising the following operably linked elements:

(a) a transcription promoter;

(b) a DNA segment (I); and

(c) a transcription terminator;

(5) an antibody that binds to an epitope of the polypeptide (II); and

(6) a culture cell containing (IV).

USE - (I) can be used to screen for its agonists and antagonists.

Agonists of (I) are useful for upregulating cellular or physiological responses whereas antagonists are used to down-regulate these activities.

The **PAR4** polypeptide is further useful for dissecting the

effects of **thrombin** or other **activating**

proteases in the clotting **pathway** from the effects of

these **proteases** at the cellular level. Agonists are specifically

useful in promoting the proliferation and/or differentiation of

platelets, in mediating inflammatory events, responses to vascular

injury, chemotaxis or mitogenesis, and in producing growth factors.

Antagonists are useful as research reagents for characterizing sites of ligand-receptor interaction.

Dwg.0/1

FS CPI

FA AB; DCN

MC CPI: B04-C01G; B04-E03D; B04-G04; B04-K01R; B04-L01; B04-L06; B04-N04A;
B11-C07A; B11-C08E4; **B12-K04E**; **B12-K04F**; B14-F02;
D05-H08; **D05-H09**; D05-H11; D05-H12A; D05-H12E; D05-H13;
D05-H14; D05-H17A4

TECH UPTX: 19991221

TECHNOLOGY FOCUS - BIOTECHNOLOGY - The isolated **PAR4** polypeptide

(I) comprises nucleotides 227 to 1330, preferably nucleotides 317 to 1330 of the 4895 base pair sequence fully defined in the specification.

ABEX UPTX: 19991221

SPECIFIC SEQUENCES - The isolated **PAR4** polypeptide (I) comprises amino acids 18 to 385 of the 385 amino acid sequence fully defined in the specification, or its derivatives.

EXAMPLE - An EST sequence was identified using a database that showed homology to the three **protease-activated**

receptors in the fourth transmembrane domain. A 600 base pair DNA

probe derived from this sequence was used to screen a selected lymphoma

Daudi cell line cDNA library, by standard techniques. cDNA inserts were

sequenced on both strands by the chain termination method, using the

Sequenase Kit (US Biochemicals). A full length cDNA clone was identified,

sequences on both strands and designated **protease-**

activated receptor 4 (PAR4).

L84 ANSWER 12 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 1999-619953 [53] WPIX

DNN **N1999-457240** DNC **C1999-180904**

TI DNA molecules encoding **protease-activated receptor 4**, useful in compound assays for **thrombin** agonist and antagonist activity.

DC B04 D16 S03

IN COUGHLIN, S R; KAHN, M

PA (REGC) UNIV CALIFORNIA

CYC 24

PI WO 9943809 A2 19990902 (199953)* EN 69p C12N015-12
 RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
 W: AU CA JP KR NO
 AU 9926728 A 19990915 (200004)
 NO 2000004274 A 20001013 (200063) C12N000-00
 EP 1056854 A2 20001206 (200064) EN C12N015-12
 R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
 KR 2001041418 A 20010515 (200167) C12N015-12
 JP 2002504369 W 20020212 (200215) 82p C12N015-09

ADT WO 9943809 A2 WO 1999-US2983 19990211; AU 9926728 A AU 1999-26728 19990211; NO 2000004274 A WO 1999-US2983 19990211, NO 2000-4274 20000825; EP 1056854 A2 EP 1999-906934 19990211, WO 1999-US2983 19990211; KR 2001041418 A KR 2000-709552 20000828; JP 2002504369 W WO 1999-US2983 19990211, JP 2000-533549 19990211

FDT AU 9926728 A Based on WO 9943809; EP 1056854 A2 Based on WO 9943809; JP 2002504369 W Based on WO 9943809

PRAI US 1998-32397 19980227

IC ICM C12N000-00; C12N015-09; C12N015-12

ICS A61K038-00; A61K038-17; A61K038-48; A61K045-00; A61P007-02; A61P009-10; A61P017-02; A61P029-00; C07K014-705; C07K016-28; C12N001-19; C12N001-21; C12N005-10; C12N009-74; C12Q001-00; G01N033-68

AB WO 9943809 A UPAB: 19991215

NOVELTY - Nucleic acids encoding a **protease-activated receptor 4 (PAR4)** and the corresponding recombinant polypeptides, are new.

DETAILED DESCRIPTION - The DNA encodes an amino acid sequence of 397 (I) or 386 (II) amino acids (aa; given in the specification) and has sequence of 1360 (III) or 1534 (IV) base pairs (bp; given in the specification) or degenerate sequences of (III) and (IV).

INDEPENDENT CLAIMS are also included for the following:

- (1) a purified DNA which has 50 % or greater identity to (III) or (IV) and where the DNA selectively hybridises to sequences complementary to (III) and (IV);
- (2) an isolated **PAR4** polypeptide;
- (3) a purified polypeptide (A) which is **activated** by **thrombin** and mediates phosphoinositide hydrolysis in a cell expressing the polypeptide on its surface;
- (4) a fragment or analog of a polynucleotide encoding the purified polypeptide;
- (5) a purified **PAR4** activating peptide;
- (6) an antibody which selectively binds to (A);
- (7) a vector comprising the DNA of (III) or of claim (1);
- (8) a cell comprising the vector of claim (7); and
- (9) an assay device comprising a support surface and a cell of claim (8) or membranes derived from the cell of (8).

ACTIVITY - Cardiant; coagulant; anticoagulant; antiarteriosclerotic; anti-inflammatory; nephrotropic; hemostatic; vulnerary.

MECHANISM OF ACTION - **Thrombin-PAR4** interaction promoter and/or inhibitor.

USE - The recombinant **receptor** polypeptides, **receptor** fragments and analogs expressed on the surface of cells are useful in methods for screening candidate compounds for their ability to act as agonists or antagonists to the effects of the interaction between **thrombin** and **PAR4**. Reaction-agonists may be

used as therapeutics to treat wounds, promote clotting and as reagents to **activate platelets** in diagnostic tests. Reaction-antagonists may be used to control blood coagulation, treat heart attacks and strokes and block inflammatory and proliferative responses to injury (as occur in normal wound healing and variety of diseases including atherosclerosis, restenosis, pulmonary inflammation (ARDS) and glomerulosclerosis). Antibodies of the invention are immunoreactive or immunospecific for and therefore specifically bind to a **PAR4** protein and may be used as screening agents or reaction antagonists.

The **PAR4 receptor** is **activated** by **thrombin** with subsequent phosphoinositide hydrolysis, Ca^{2+} efflux and **platelet aggregation**. **Activation** of leukocytes, mesenchymal cells in response to wounding also occurs as well as mediating signaling in embryonic development. The ability of **PAR4** to mediate signaling by **alpha -thrombin** was tested. *Xenopus* oocytes were microinjected with mouse **PAR4** cRNA. This conferred **thrombin**-dependent ^{45}Ca mobilization which reflected agonist-triggered phosphoinositide hydrolysis.

ADVANTAGE - A novel **thrombin receptor** **PAR4** is disclosed making it possible to identify novel **thrombin** agonists and antagonists which may not be identifiable via **PAR1**, **PAR2** or **PAR3** receptors. This **receptor** also makes it possible to obtain additional information regarding **thrombin activation** and the sequence of biochemical events initiated.

Dwg:0/15

FS CPI EPI

FA AB; DCN

MC CPI: B04-C01G; B04-E02F; B04-E05; B04-E08; B04-F0100E; B04-F0700E; B04-G04; B04-G0400E; B11-C07A; B11-C08E5; **B12-K04E**; **B12-K04F**; B14-C03; B14-F01B; B14-F04; B14-F07; B14-F08; B14-L01; B14-L02; B14-N17B; D05-C12; **D05-H09**; D05-H11; D05-H12A; D05-H12B; D05-H12D1; D05-H12E; D05-H14; D05-H17A6; D05-H18B
EPI: S03-E14H

TECH UPTX: 19991215

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Polypeptide: The purified polypeptide of (3) has the sequence of (I) or (II).

Preparation: The DNA, **receptor** or **receptor** fragment is derived from a vertebrate animal, preferably a human or mouse. However, the gene can be chemically synthesized.

ABEX UPTX: 19991215

SPECIFIC SEQUENCES - (I) represents an amino acid sequence of a **PAR4** protein comprising a disclosed sequence of 397 amino acids. (II) represents an amino acid sequence of a **PAR4** protein comprising a disclosed sequence of 386 amino acids. (III) represents a polynucleotide sequence encoding **PAR4** comprising a disclosed sequence of 1360 bp. (IV) represent a polynucleotide sequence encoding **PAR4** comprising a disclosed sequence of 1534 bp.

EXAMPLE - The public expressed sequence tag (EST) database was searched for potential **PAR** sequences by identifying sequences with homology to **PAR1**, **PAR2** and **PAR3**. One EST clone, 400689, was identified showing similarity over an eleven amino acid stretch and was further characterized. The EST sequence was used to obtain mouse and human cDNA and genomic clones by a combination of PCR and hybridization techniques. The human **PAR4** sequence was obtained using degenerate PCR primers to amplify a 900 bp dominant product from total human genomic DNA. PCR was performed and sequencing of the 900 bp products revealed a novel amino acid sequence that was 88 % identical to mouse **PAR4**. Human megakaryocytic cell lines were screened for **PAR4** expression by Northern analysis using the 900 bp product as a probe and the K562 erythroleukemia cell line was found to be positive. 5'RACE and nested PCR reactions using two reverse primers were performed.

A dominant 350 bp band was observed, subcloned and sequenced, providing the sequence to the hPAR4 start codon. The same kit and template were used for 3'RACE. The GIBCO UAP primer was used as a reverse primer and hemi-nested PCR was then performed. A dominant 1.6 kb band was observed, subcloned and sequenced, and provided the sequence for a stop codon. A functional hPAR4 clone was created by PCR using Vent polymerase with primers from the start codon to 50 bp beyond the stop codon using 25 cycles of PCR and K562 template cDNA. The PCR product was sequenced and subcloned into an oocyte expression vector for generating cRNA (pFROGGY). Human **PAR4** cRNA was microinjected into *Xenopus* oocytes to study its function.

L84 ANSWER 13 OF 13 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN
 AN 1998-271905 [24] WPIX
 DNN N1998-213491 DNC C1998-084844
 TI DNA encoding **protease-activated receptor 3** -
 for detection of specific agonists and antagonists, potentially useful for
 treating e.g. **thrombosis**, atherosclerosis, inflammation etc..
 DC B04 D16 S03
 IN CONNOLLY, A; COUGHLIN, S R; ISHIHARA, H
 PA (REGC) UNIV CALIFORNIA
 CYC 21
 PI WO 9818456 A1 19980507 (199824)* EN 74p A61K031-00
 RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
 W: CA JP
 US 5892014 A 19990406 (199921) C12N015-12
 EP 948323 A1 19991013 (199947) EN A61K031-00
 R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
 JP 2001510988 W 20010807 (200150) 74p C12N015-09
 ADT WO 9818456 A1 WO 1997-US19732 19971029; US 5892014 A US 1996-742440
 19961030; EP 948323 A1 EP 1997-946388 19971029, WO 1997-US19732 19971029;
 JP 2001510988 W WO 1997-US19732 19971029, JP 1998-520768 19971029
 FDT EP 948323 A1 Based on WO 9818456; JP 2001510988 W Based on WO 9818456
 PRAI US 1996-742440 19961030
 IC ICM A61K031-00; C12N015-09; C12N015-12
 ICS A61K035-00; A61K038-00; A61K045-00; A61P007-02; C07K014-435;
 C07K014-705; C12N001-15; C12N001-19; C12N001-21; C12N005-10;
 C12N015-63; C12P021-02; C12Q001-34; G01N033-15; G01N033-50;
 G01N033-53; G01N033-566
 AB WO 9818456 A UPAB: 19991122
 DNA (I) encoding a **protease-activated receptor**
 3 (**PAR3**) is new.
 Also claimed are:
 (1) an isolated **PAR3** protein (II), and its fragments or
 homologues that include a domain **activatable** by **thrombin**
 and mediate hydrolysis of phospho-inositide (PI);
 (2) a vector containing (I);
 (3) a cell containing (2);
 (4) an assay device containing these cells on a support surface;
 (5) a composition containing an (ant)agonist of **PAR3** ligand
 (**PAR3L**; especially **thrombin**) plus a carrier.
 USE - Cells of (3) are used to screen for (ant)agonists of **PAR3L**.
 (II) and agonists are useful in treatment of **thrombosis**,
 atherosclerosis, re-stenosis and other **thrombin**-related
 diseases.
 Antagonists are potentially useful for mediating inflammatory and
 proliferative responses to injury (as in normal wound healing), also
 atherosclerosis, re-stenosis, pulmonary inflammation and
 glomerulo-sclerosis, and formation of clots that cause stroke and heart
 attacks.
 Agonists and antagonists are preferably administered intravenously,
 but may also be given orally, nasally or topically.
 ADVANTAGE - Cells of (3) allow identification of (ant)agonists that

can not be identified by PAR1 or 2.

Dwg.6/10

FS CPI EPI

FA AB; GI

MC CPI: B04-E01; B04-E08; B04-F01; B04-K01; B12-K04; B14-C03;
B14-F04; B14-F07; B14-N10; D05-H09; D05-H10; D05-H12A;
D05-H12E; D05-H14
EPI: S03-E14H4

=> d his

(FILE 'HOME' ENTERED AT 06:14:06 ON 09 MAR 2004)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 06:14:23 ON 09 MAR 2004

L1 1 S US20020103107/PN
E SOSLAU G/AU
L2 42 S E3-E5
E (GP OR GLYCOPROTEIN OR GLYCO PROTEIN) () (IB OR 1B OR (I OR 1) ()
L3 2133 S (GP OR GLYCOPROTEIN OR GLYCO PROTEIN) () (IB OR 1B OR (I OR 1) ()
E GLYCOPROTEIN/CT
E E57+ALL
L4 364 S E2
L5 724 S GLYCOPROTEIN#/CW (L) (1B OR IB OR GP1B OR GPIB)
E PAR/CT
E E6+ALL
L6 280 S E2
L7 308 S E5
L8 50 S E7
L9 92 S E9
L10 13417 S (PAR OR ((PROTEINASE OR PROTEASE) () ACTIVAT? () RECEPTOR) (5A) (1
L11 13414 S (PAR OR ((PROTEINASE OR PROTEASE) () ACTIVAT? () RECEPTOR) () (1 OR
L12 10684 S L10,L11 NOT RECEPTOR
L13 2733 S L10,L11 NOT L12
L14 4881 S L3-L9,L13
E DRUG SCREENING/CT
L15 22652 S E3-E5
E E3+ALL
L16 28787 S E2,E1+NT
E E5+ALL
L17 7824 S E3
E E14+ALL
L18 3025 S E1
E E2+ALL
E DRUG/CT
E E10+ALL
L19 15561 S E3
E DRUG/CT
L20 882 S E13
L21 8110 S E230+NT OR E231
L22 4500 S E262 OR E263
E DRUG SCREENING+ALL/CT
E E7+ALL
L23 156 S E2
L24 78 S L14 AND L15-L23
L25 137 S L14 AND SCREEN?
L26 163 S L24,L25

FILE 'REGISTRY' ENTERED AT 06:26:53 ON 09 MAR 2004

L27 1 S THROMBIN/CN

FILE 'HCAPLUS' ENTERED AT 06:27:59 ON 09 MAR 2004

L28 16686 S L27
 L29 31055 S THROMBIN
 L30 118 S BLOOD() (COAGULAT? OR CLOT?) () FACTOR() (IIA OR II() ACTIVAT?)
 L31 463 S THROMBASE OR THROMBINAR OR THROMBOFORT OR THROMBOSTAT OR TROP
 L32 31683 S L28-L31
 L33 48 S L26 AND L32
 L34 33 S L26 AND PLATELET(L) AGGREGAT?
 E CELL AGGREGATION/CT
 L35 7 S E3,E4 AND L26
 E E3+ALL
 L36 15 S E1+NT AND L26
 E PLATELET/CT
 L37 30 S L26 AND E3-E27
 E E28+ALL
 L38 7 S L26 AND E3
 E PLATELET/CT
 E E33+ALL
 L39 16 S L26 AND E6,E5
 E E4+ALL
 L40 27 S L26 AND E5,E4+NT
 L41 40 S L26 AND (E12+NT OR E13+NT OR E14+NT)
 L42 11 S L26 AND (E16+NT OR E17+NT)
 L43 20 S L26 AND (ANTITHROMBO? OR ANTIPLATELET? OR ANTI() (THROMBO? OR
 L44 92 S L33-L43
 L45 1 S L2 AND L26
 L46 1 S L2 AND L44
 L47 1 S L1,L45,L46
 L48 41 S L2 NOT L47
 SEL DN AN 1 3 10 18
 L49 4 S E1-E12 AND L48
 L50 5 S L47,L49
 L51 91 S L44 NOT L50
 L52 32 S L41 AND (PY<=2000 OR PRY<=2000 OR AY<=2000)
 SEL DN AN L52 4 7 19 26 28
 L53 5 S E13-E27
 L54 10 S L50,L53
 L55 59 S L51 NOT L52-L54
 SEL DN AN L55 7 14-18 23 27 29 30 32 33 35 40-43
 L56 17 S E28-E70
 L57 27 S L54,L56 AND L1-L26,L28-L56
 L58 27 S L57 AND (PAR# OR PAR() (1 OR 2 OR 3 OR 4) OR PLATLET?(L) ACTIVA
 L59 27 S L58,L***

FILE 'REGISTRY' ENTERED AT 07:06:59 ON 09 MAR 2004

FILE 'HCAPLUS' ENTERED AT 07:07:09 ON 09 MAR 2004

FILE 'BIOSIS' ENTERED AT 07:07:53 ON 09 MAR 2004

E SOSLAU G/AU
 L60 67 S E3,E4
 L61 30 S L60 AND (00520/CC OR (CONGRESS? OR CONFERENCE? OR POSTER? OR
 L62 4 S L61 AND ARTICLE/DT
 L63 26 S L61 NOT L62
 SEL DN AN L63 1-3 5 7 8 11
 L64 7 S L63 AND E1-E14

FILE 'BIOSIS' ENTERED AT 07:12:26 ON 09 MAR 2004

FILE 'WPIX' ENTERED AT 07:12:50 ON 09 MAR 2004

L65 595 S C12Q001-56/IC,ICM,ICS
 L66 1482 S L3/BIX
 L67 45 S ((PROTEINASE OR PROTEASE) () ACTIVAT? RECEPTOR?)/BIX
 L68 161 S (PAR1 OR PAR2 OR PAR3 OR PAR4 OR PAR() (1 OR 2 OR 3 OR 4))/BIX

L69 365 S ((ALPHA OR ALFA OR BETA OR GAMMA) (S) THROMBIN) /BIX
L70 22 S L65 AND L66-L69
L71 0 S L65 AND L67
L72 1 S L65 AND L68
L73 5 S ((ALPHA OR ALFA OR BETA OR GAMMA) () THROMBIN) /BIX AND L65
L74 7 S L67,L68 AND (B04-H19 OR C04-H19 OR B04-B04D3 OR C04-B04D3) /MC
SEL DN AN 1 3-5
L75 4 S E15-E23
L76 4 S L72,L75
E SOSLAU G/AU
L77 2 S E3
L78 5 S L76,L77
L79 5 S L78 AND (PAR# OR PLATELET? OR ACTIVAT? OR RECEPTOR OR GP? OR
L80 33 S L67,L68 AND (B12-K04# OR C12-K04# OR D05-H09) /MC
L81 30 S L80 NOT L70-L79
SEL DN AN 1 4 9 12 14 25 26 28
L82 8 S E1-E21
L83 8 S L82 AND (PAR# OR PLATELET? OR ACTIVAT? OR RECEPTOR OR GP? OR
L84 13 S L79,L83 AND L65-L83

FILE 'WPIX' ENTERED AT 07:41:09 ON 09 MAR 2004

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